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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. ER 871777792 US

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Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

2,4- and 3,6-Disubstituted Pyran Biomimetics of cis-3,6-Disubstituted Piperidine...

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* _____
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☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number _____
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METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees.
☒ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 50-0720
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.
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Respectfully submitted,

SIGNATURE _____

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Date April 16, 2004

REGISTRATION NO. 28,664 *(if appropriate)*

Docket Number: RM.WSQ

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATT'Y. DKT.	:	RM.WSQ
APPLICANT	:	Aloke K. Dutta
SERIAL NO.	:	
FILED	:	April 16, 2004 (By Express Mail)
FOR	:	2,4- and 3,6-Disubstituted Pyran Biomimetics of cis-3,6-Disubstituted Compounds that Interact with Monoamine Transporters

CERTIFICATE OF MAILING
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I hereby certify that a Provisional Application Under 37 C.F.R. § 1.53(b)(2) in the name of inventor Aloke K. Dutta, a Provisional Application Cover Sheet, Specification (73 pages), PTO Form 1595 and an executed Assignment document are being deposited with the United States Postal Service under 37 C.F.R. § 1.10 as Express Mail Post Office to Addressee on the date indicated hereinabove and addressed to Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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2,4- and 3,6-Disubstituted Pyran Biomimetics of cis-3,6-Disubstituted Compounds that Interact with Monoamine Transporters

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Abstract:

In our effort to delineate novel pharmacophoric configuration of bioisosteric pyran version of cis-3,6-disubstituted piperidine derivatives, further structure activity relationship study was carried out. Both cis and trans 2,4- and 3,6-disubstituted derivatives were synthesized to determine positional importance of N-substitution on activity. All novel compounds were tested for their affinity at the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) in the brain by measuring competition for the binding of [^{3}H]WIN 35 428, [^{3}H]citalopram and [^{3}H]nisoxetine respectively. Selected compounds were also evaluated for their activity in inhibiting the uptake of [^{3}H]DA. Our binding results demonstrated activity in 3,6-disubstituted derivatives while 2,4-disubstituted derivatives failed to exhibit any appreciable binding activity. Further structure exploration of the exocyclic N-atom in 3,6-disubstituted derivatives produced compounds potent at both DAT and NET. Compounds **16h** and **16o** with hydroxyl and amino groups in the phenyl moiety of the benzyl group produced the highest activity for the NET. In this regard, compound **16e** with the methoxy substituent produced weak activity at NET which upon conversion into hydroxyl functionality as in **16h** produced potent activity for the NET. Various indole derivatives produced different interactions; the 5-substituted indole derivative **16n** produced potent activity at NET, confirming the bioisosteric equivalence between this indole moiety and the phenyl-4-hydroxy group in **16h**.

TITLE: 2,4- and 3,6-Disubstituted Pyran Biomimetics of cis-3,6-Disubstituted Piperidine Compounds that Interact with Monoamine Transporters

PART I

Introduction

Cocaine, a naturally occurring alkaloid, is well known for its powerful abuse and addiction potential. Addiction to cocaine is a major problem in our society today, inflicting severe medical, social, judicial and financial costs.[1,2] Currently, no effective medication is available for the treatment of cocaine addiction and there is an urgent need to develop a

suitable medication to treat this chronic disorder.[3]

Extensive studies have been conducted so far to understand the mechanism of action of cocaine which might eventually lead to development of a much needed medication for cocaine dependence. Cocaine binds to the all three monoamine transporter systems in the brain but its central reinforcing action is thought to be derived mainly from binding to the dopamine transporter (DAT).[4-7] This role of DAT is strongly supported by various experimental evidences.[8-10] However, this does not rule out the involvement of non-dopaminergic systems in cocaine reward pathway as for example the serotonergic system has been shown to modulate some of cocaine's effects.[11,12]

Many efforts have been directed towards development of molecules targeting DAT and a great number of structurally diverse compounds have already been synthesized with an aim to develop effective pharmacotherapies for cocaine addiction. These compounds include tropane, benztropine, mazindol, or methylphenidate derivatives, and also piperazine or piperidine derivatives of GBR 12935. Detailed description of SAR studies on these compounds is provided in the recent review papers.[13-15] The existence of this wide variety of molecular structures might indicate the existence of flexible binding pockets in the DAT which can accommodate different molecular templates. Our efforts to develop molecules targeting DAT started with piperidine analogs of GBR 12909. A large number of potent and selective piperidine analogs have been synthesized and biologically characterized.[16-19] Most of these molecules possess a high degree of structural flexibility, and consequently, it was difficult to elucidate their biologically active conformation for interacting with the DAT. Recently, we converted one of our lead piperidine analogs into structurally constrained 3,6-disubstituted piperidine derivatives possessing cis- and trans-structures.[20] The results demonstrated that preferential affinity for the DAT lied with the cis-structure compared to the trans-structure (Figure 1). Further SAR study on this cis-template produced derivatives with higher affinity for the DAT confirming this cis-structure as a novel template for the DAT.[21]

In a recent preliminary study, we demonstrated that the piperidine ring in our structurally constrained 3,6-disubstituted piperidine derivatives can be replaced by a pyran moiety while preserving DAT activity with the same stereochemical cis-structural preference (Figure 2).[22] However, the relative activity was some what greater in the piperidine derivatives indicating the potential importance of the more basic N-atom in interaction with DAT. Our earlier study reported the synthesis and biological characterization of trans-3,6-disubstituted pyran derivative and a limited number of cis-3,6-

disubstituted pyran derivatives. The cis derivative was approximately two times as potent as the trans compound. In previous studies with tropane and benztropine analogs, transformation of certain DAT selective 3-aryltropane and benztropine analogs into oxy-3-aryltropane and oxy-benztropine analogs were carried out which resulted in production of divergent results.[23,24] Transformation of tropane to oxy-3-aryltropane had minimal influence on activity for the DAT compared to its parent bioisosteric N-analogue.[23] On the other hand, similar transformation of benztropine to oxy-benztropine analogs resulted in loss of potency for the DAT.[24] Both oxy-3-aryltropane and oxy-benztropine have constrained tetrahydro-pyran moiety albeit oxy-3-aryltropane analogs contain additional substitutions. These results point to the N-atom in benztropine as a critical requirement for binding to the DAT, whereas the N-atom in 3-aryltropane analogs may not be so critical, consonant with the existence of flexible binding pockets in the DAT. This result also indicates that a structurally constrained pyran moiety requires more molecular specificity for exhibiting activity at DAT compared to a structurally constrained piperidine motif. These differences in activity at the DAT might be due to the fact that several changes could occur in the pharmacodynamic properties upon the replacement of an N-atom by a less basic O-atom. Consequently, different modes of interaction with DAT could occur for pyran and their bioisosteric piperidine counterparts. These two types of compounds may also produce different pharmacokinetic properties.

In our current study we wanted to explore further substitution on the exocyclic N-atom in 3,6-disubstituted derivatives to gain more insight in molecular determinants required for activity. In addition, we wanted to map out the positional requirement of the amino moiety on the pyran ring for interaction with the DAT by varying its location. For this purpose, we have designed, in addition to 3,6-disubstituted derivatives, 2,4-disubstituted pyran derivatives in their cis- and trans-isomeric forms. The results from these studies will shed more light on the dynamics of molecular interaction of these novel pyran derivatives with the monoamine transporters.

Chemistry

Target compounds **7a,b** and **16a-p** were synthesized by following synthetic procedures shown in **Scheme 1** to **Scheme 5**.

Synthesis of the target compounds **7a** and **7b,** shown in **Scheme 1,** was accomplished in high yields by following efficient synthetic routes. The basic pyranose ring structure in compound **2** was achieved by [4+2] Hetero-Diels-Alder cycloaddition of Danishefsky's diene and aldehyde **1** in the presence of $BF_3 \cdot Et_2O$ which produced **2** in 80%

yield.[25,26] Reduction of **2** with $NaCNBH_3$ in presence of BF_3-Et_2O in THF produced racemic cis- and trans-mixture of **3a** and **3b** (2.5:1) in 96% yield. The two isomers were separated by careful flash chromatography, and their structures were assigned by NMR and NOE (see supplemental materials). Compounds **6a** and **6b** were synthesized from **3a** and **3b** respectively in high yields by three steps which involve first mesylation with methanesulfonyl chloride in dry dichloromethane to produce **4a** and **4b** which was followed by treatment with sodium azide in DMF with inversion of configuration to produce azides **5a** and **5b**.[27] This azido displacement reaction resulted in production of the cis-isomer **5a** from *trans*-**4a** and the trans-isomer **5b** from *cis*-**4b**. Finally, catalytic hydrogenation of the azides **5a** and **5b** with Pd/C produced the amine precursors **6a** and **6b** in good yield. Reductive amination of **6a** and **6b** by following a procedure described by us earlier furnished **7a** and **7b**, respectively, in 72.6% and 54% yield.

Scheme 2 delineates the preparation of the key pyran 3,6-disubstituted intermediate **11** with trans-stereochemistry. Briefly, aldehyde **1** was converted into **8** by reacting with the in situ prepared Grignard reagent, prepared from 4-bromo-1-butene and magnesium in dry ether in 91% yield. O-vinyllation of **8** with ethyl vinyl ether in the presence of $Hg(OCOCF_3)_2$ at room temperature produced **9** in 66% yield.[28] Ring closing metathesis of **9** in presence of a Grubb's catalyst in refluxing benzene afforded olefin **10** in 92.6% yield.[29,30] Hydroboration of **10** with 9-BBN in THF, followed by oxidation gave exclusively *trans*-isomer **11** in 93.5% yield.[31] Compound **11** was used next as a starting precursor for the synthesis of various derivatives with different substitutions at the exocyclic N-atom as shown in the scheme **3** and scheme **4**. First, compound **11** was subjected to Swern oxidation reaction condition which produced ketone **12** in 91% yield. Reductive amination of **12** with 4-fluorobenzylamine produced **16a** as a major product in 45% yield (Scheme 3). As described in the synthesis of compound **6a-b** in **Scheme 1**, compound **11** was next converted into a cis-amine intermediate **15** via three steps consisting of first mesylation with methanesulfonyl chloride in dry dichloromethane followed by substitution with sodium azide in DMF and finally, catalytic hydrogenation with Pd-C in methanol. Reductive amination of **15** with various aldehydes furnished target compounds **16b-n** in good yield (**Scheme 4**).

The synthesis of compounds **16o** and **16p** is described in **Scheme 5**. **16o** was synthesized by the reduction of **16d** with Tin (II) chloride dihydrate in ethanol and ethyl acetate in 60% yield. Amide Intermediate **17** was obtained from the reaction of amino-compound **15** with 4-fluoro-phenylacetyl chloride. Reduction of **17** with freshly generated

borohydrate gave the target compound **16p**.

Results and Discussions:

As a part of extension of our studies on structurally constrained piperidine derivatives, we have developed novel 3,6-disubstituted pyran molecules as potential blockers for monoamine transporters. Preliminary binding results of the compounds at monoamine transporters indicated a positive correlation with the results for our structurally constrained 3,6-disubstituted piperidine template including the cis-isomeric preference. However, in comparison to their piperidine counterparts, these compounds were some what less potent at DAT. This might indicate that even though the N- and O-atoms in the piperidine and pyran rings are bioisosteres, the existence of different interaction modes with the monoamine transporter systems can not be ruled out as the physical properties such as basicity of these two atoms are quite different. Consequently, in our current SAR study we wanted to examine additional derivatives. These derivatives were synthesized by functionalizing the exocyclic N-atom with various bioisosteric heterocyclic moieties and other substituted benzyl derivatives. Results from these derivatives will allow us to compare directly and clearly any similarity and dissimilarity in molecular interaction between the piperidine and pyran series of compounds which in turn could provide a unique pharmacophoric models for pyran derivatives. Thus, in this report, further SAR exploration on our initial lead pyran structure was taken up to better understand its optimal pharmacophoric requirement and functional properties in interacting with the monoamine transporter systems.

Additionally, we wanted to investigate the positional importance of the exocyclic N-substituted moiety on the pyran ring. This exploration was thought to be necessary since any loss in potency from transformation of piperidine to pyran moiety might lead to a less than optimal interaction at the 3-amino substituent site on the pyran ring. This could potentially arise as the O-atom in pyran ring, being less basic than the piperidine N-atom, may interact with different residues at the DAT. An adjacent positional shift of this N-substituent could compensate for this leading to enhanced interaction. Moreover, testing the effect of positional shift of the amino substituent will also answer the question of whether the 3,6-disubstituted configuration is required as an optimal pharmacophore for binding interaction. In an attempt to address this question, 2,4-disubstituted derivatives in their cis- and trans-forms were designed and synthesized. The binding results from these molecules will enable us to understand the geometrical and positional requirements in these new pyran templates for binding interaction.

Following synthesis of 2,4-disubstituted cis and trans compounds **7a** and **7b**, they were characterized in binding assays for the three monoamine transporters (Table 1). Results indicated that the positional change from 3,6-disubstitution to 2,4-disubstitution adversely affected the binding activity of these two molecules. It is interesting to note that even though the activity was low, the preferential affinity for the DAT was still exhibited in the cis version. These results confirmed that the *cis*-3,6-disubstituted pyran template is a basic pharmacophoric requirement for interaction with DAT.

In the 3,6-disubstituted version, as we reported in our preliminary communication,[22] replacement of the fluoro-substituent by electron withdrawing substituents resulted in more potent compounds for the DAT as illustrated in the cyano-substituted molecule **16c** and nitro-substituted molecule **16d**. Nitro-substitution produced the most active compound among these synthesized analogs for the DAT (IC50 = 38.3 nM). This trend agreed with our previous data for the piperidine counterparts. On the other hand, electron donating methoxy substitutent in **16e** produced comparable potency at the DAT (IC_{50} = 84 nM).[22] Same relative differences in potency was observed for piperidine derivatives.[21] Introduction of 3,4-difluoro substituents in **16j** reduced potency at all three transporters compared to the 4-fluoro **16b**. With the dichlorosubstituted compound **16i**, no improvement in activity was observed compared to unsubstituted **16k**, suggesting a different mode of binding interaction compared to tropane- and methylphenidate-type of compounds.[32,33] As far as other halogen derivatives are concerned, the bromo compound **16l** exhibited somewhat higher activity at DAT compared to unsubstituted **16k** whereas the iodo compound **16m** displayed comparable potency.

Compared to the methoxy substituted compound **16e**, the hydroxy substituted compound **16h** retained the activity at DAT (IC50 = 78.4 nM for **16h** and IC50 = 84nM for **16e**), but its selectivity was shifted in favor of NET shown by the much higher activity at NET (IC50 = 22.6 nM for the NET, NET/DAT = 0.29) (Table 2). The amino-substituted compound **16o** also exhibited high potency at NET. These two substitutents can act as both hydrogen-bond donor or acceptor site, although in different capacity. The big shift towards activity and selectivity at NET caused by these two polar substitutents might indicate a critical involvement of hydrogen bond in interaction with NET. However, similar results were not observed in the structurally constrained piperidine analogs, reflecting the existence of different interaction modes between these two templates.[21] Since a high degree of homogeneity has been demonstrated between the DAT and NET structural sequence, it is of interest to observe that a subtle change in pyran structure can induce

differential interactions in favor of the NET.[34,35]

In order to gain further insight into the nature of hydrophobic interaction of aromatic moiety, we decided to replace the phenyl aromatic moiety in the benzyl group by bioisosteric indole moieties. Thus, replacement with a 2- and 3-indole moiety as illustrated in compounds **16g** and **16f,** led to moderate to diminished potency at DAT. Interestingly, as was seen with our piperidine derivative counterparts, the 2-indole substituted derivative **16g** was 3.5 fold more active at DAT compared to the 3-substituted **16f** (227 vs. 794 nM) and was also more active than the unsubstituted **16k**. A similar increase in affinity for the NET was also observed for the 2-substituted indole compared to the 3-substituted compound (401 vs. 1860 nM). In our further attempt to test the importance of the position of the indole N-atom along with hydrophobic interaction, the 5-substituted indole derivative **16n** was designed and synthesized. In this regard, 5-substitution was chosen as it will assume bioisosteric configuration of the p-hydroxy-phenyl moiety of **16h**. The binding results for **16n** indicated high affinity, similar to **16h**, for the NET, indicating the involvement of H-bonding with the indole amino moiety. This result further demonstrates the existence of a H-bond donor or acceptor site in the NET which, when oriented correctly with respect to ligand's H-bond forming functionality, can provide potent interaction.

In compound **16p**, the fluorobenzyl moiety was replaced by a 4-fluorophenylethyl moiety which did not result, surprisingly, in decreased activity at DAT compared to **16b**. This result was in contrast to the results observed in the constrained piperidine counterpart where a drop in DAT activity resulted from such modification.[21] This result likely indicates that a different pharmacophoric optimization required, probably via a distance geometry approach, to produce optimum activity in the pyran template. As we expected, the exocyclic-N-substituion with an aromatic moiety is necessary in pyran derivatives for their activity at the monoamine transporter systems, as compound **15** exhibited little or no activity at the DAT.

Selected compounds with relatively higher activity at the DAT were tested in the DA uptake assay. For the most part no differential uptake and binding activity was observed with the exception of compound **16d** which showed a three fold higher potency in inhibiting binding than uptake.

Molecular Modeling:

In order to demonstrate a difference in spatial distribution in the lowest energy conformers between 3,6-disubstituted and 2,4-disubstituted pyran derivatives, we have carried out a preliminary molecular modeling study. 2,4-Disubstituted compound **7a** and

the 3,6-disubstituted compound **16b** were chosen for this study. Compounds were minimized first with the SYBYL molecular modeling program (version 6.9, 2002, Tripos Associates, Inc., St. Louis, MO). Minimized molecules obtained from this operation were next subjected to a grid search protocol to search for the lowest energy conformer. Grid search operation was carried out with the change of torsional angle from 0° to 360° with an increment of 10° comprising of atoms α–β–γ–δ as shown in Figure 3A and 3B for both **7a** and **16b**. This operation resulted in the generation of 3.16 Kcal/mole lowest energy for **7a** with a corresponding torsional angle of 77.8 ° and 5.61 Kcal/mole for **16b** with a torsional angle of 300°. In the final step, the two minimized structures were overlapped with the alignment program (see Figure 3C). It was quite evident that the exocyclic amino substituents in the two compounds were oriented very differently in two different directions.

Conclusion:

In this report, we have outlined the cis-3,6-disubstituted tetrahydro-pyran template as a pharmacophore for activity at the monoamine transporter systems. SAR exploration with this template with various substituents on the exocyclic N-atom produced potent activities at both DAT and NET. Compound **16d** with the electron withdrawing nitro-substituent turned out to be the most active for the DAT. Interestingly, the compounds **16h** and the **16o** with para-hydroxy and para-amino substituents exhibited high potency for the NET, indicating formation of H-bonding. This was further confirmed by the bioisosteric version **16n** which exhibited strong selective potency at NET. The SAR results for the current pyran molecules do not correspond with those for the piperidine derivatives, indicating differential interaction modes with monoamine transporters. Our ongoing studies at different molecular centers on this pyran ring to probe and identify optimum pharmacophoric structure will shed more light on their nature of interaction with monoamine transporters.

Experimental Details

Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. Dry solvent was obtained according to the standard procedure as described in Vogel's book. All reactions were performed under inert atmosphere (N_2) unless otherwise noted. Analytical silica gel-coated TLC plates (Si 250F) were purchased from Baker, Inc and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 mM. ^1H NMR spectra were routinely obtained at GE-300 MHz and 400 MHz FT NMR.

The NMR solvent used was $CDCl_3$ as indicated. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc and were within ± 0.4% of the theoretical value.

[^{3}H]WIN 35,428 (86.0 Ci/mmol), [^{3}H]nisoxetine (80.0 Ci/mmol) and [^{3}H]dopamine (48.2 Ci/mmol) were obtained from Dupont-New England Nuclear (Boston, MA, U.S.A). [^{3}H]citalopram (85.0 Ci/mmol) was from Amersham Pharmacia Biotech Inc. (Piscataway, NJ, U.S.A.). Cocaine hydrochloride was purchased from Mallinckrodt Chemical Corp. (St. Louis, MO, U.S.A.). WIN 35,428 napthalene sulfonate was purchased from Research Biochemicals, Inc. (Natick, MA, U.S.A.). (-)-Cocaine HCl was obtained from the National Institute on Drug Abuse. GBR 12909 Dihydrochloride (1-[2-[bis(4-Fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine) was purchased from SIGMA-ALDRICH (#D-052; St. Louis, MO).

Molecular Mdeling

Molecular modeling was performed using Sybyl 6.9 software running on Silicon Graphics Octane IRIX 6.5 workstation. The compounds were sketched in appropriate stereochemistry.

First, each structure was fully minimized using standard Tripos force field with a distance –dependent dielectric function, a 0.05 Kcal/mol Å energy gradient convergence criterion was used and the six-membered pyran ring was treated as an aggregate. The Powell method was used during minimization, and charges were computed using the Gasteiger-Huckel method within Sybyl 6.9. The number of iteration was 1000. After minimization the energy for 2,4-disubstituted molecule **7a** was 5.85 Kcal/mol and the energy for 3,6-disubstituted molecule **16b** was 5.63 Kcal/mol.

In the next step, using grid search protocol, the conformational search on each minimized molecule was performed by rotating the torsion angle of compounds **7a** and **16b** formed by atoms α–β–γ–δ (see Figure 3) from 0° to 360° by 10° increments. This method was used to perform a simple systematic search such that each specified torsion angle is varied over a grid of equally space value. While searching for the lowest energy conformer, a cutoff value of 8 Kcal/mol was specified relative to the lowest conformer, and charges were computed using the Gasteiger-Huckel method. Also, the six-membered pyran ring was treated as an aggregate. For compound **7a**, a conformer with torsional angle 77.8 oC was found to have lowest energy 3.16 Kcal/mol, whereas compound **16b** produced lowest energy 5.61 Kcal/mol with a torsion angle 300° (See supplemental

materials for detail energy distribution). These two lowest energy conformers were used next for overlapping.

During overlapping, the alignment program within Sybyl6.9 was employed, and the method used was common structure method. The compound **16b** was used as template molecule and the six-membered pyran ring was used as common substructure for overlapping.

Synthesis of 2-benzhydryl-2,3-dihydro-4H-pyran-4-one (2)

A solution of boron trifluoride diethyl etherate (7.8 g, 55 mmol) in dry ether (50 ml) was added to a stirred mixture of E-1-methoxy-3-trimethylsilyloxybuta-1,3-diene(8.3 g, 48 mmol), Diphenylacetaldehyde **1** (11.4 g, 58 mmol) and dry ether (300 ml) cooled to -78° C . After one hour, the mixture was allowed to reach 0° C for three hours. The deep red reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the mixture was allowed to come to room temperature. The organic phase was separated and the aqueous phase was extracted with ether (3x70 ml). Combined the organic phase was washed with brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the crude product by chromatography (hexane/ethyl acetate 8:2) gave 2-diphenylmethyl-2,3-dihydro-4H-pyran-4-one **2** (10.2 g, 80.2%, yield) as a yellow solid.

^{1}H NMR(400Mhz, $CDCl_3$) 2.38(dd, J=3.2Hz, 16.8Hz, 1H, H-3) 2.51(m, 1H, H-3) 4.23(d, J=9.2Hz, 1H, $(Ph)_2CH$) 5.15(dt, J=3.2Hz, 8.8Hz, 1H, H-2) 5.44(d, J=6.4Hz, 1H, H-5), 7.16-7.38(m, 11H, H-6, aromatic-CH)

synthesis of *Cis* and *Trans*-2-benzhydryl-tetrahydropyran-4-ol 3a and 3b

$NaCNBH_3$ (0.75 g, 12 mmol) was added portionwise to a mixture of 2-diphenylmethyl-2,3-dihydro-4H-pyran-4-one **2** (1.05 g, 4 mmol) and boron trifluoride etherate(1.99 g, 14 mmol) in dry THF(50 ml) cooled to –78 ^{0}C. The reaction mixture was allowed to reach room temperature and the reaction was quenched with saturated aqueous $NaHCO_3$ (30 ml). The organic phase was separated, and the aqueous phase was extracted with ethyl ether (3 x 20 ml). The organic phase was combined and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure, and purification by flash chromatography (hexane/ethyl acetate 7:3) first afforded ***trans*-2-benzhydryl-tetrahydropyran-4-ol 3a** (0.73 g, 68% yield).

^{1}H NMR(400MHz, $CDCl_3$) 1.22(q, J=12Hz, 1H, H-3ax) 1.46(dq, J=4.8Hz, 12 Hz, 1H, H-5ax) 1.74-1.86(m, 2H, H-3eq, H-5eq) 3.40(dt, J=2Hz, 12Hz, 1H, H-6ax) 3.707(m, 1H, H-4) 3.941-4.039(m, 2H, H-6eq, $(Ph)_2CH$) 7.15-7.4(m, 10H, aromatic-CH).

Eluted second was ***cis*-2-benzhydryl-tetrahydropyran-4-ol, 3b** (0.3 g, 28.1 % yield). ^{1}H NMR(400MHz, $CDCl_3$) 1.5-1.58(m, 4H, H-3, H-5eq, OH) 1.84(m, 1H, H-5ax) 3.79(m, 1H, H-6eq) 3.876(d, J=8.8Hz, $(Ph)_2CH$) 3.908(dt, J=3.2Hz, 111.2Hz, 1H, H-6ax) 4.184(m, 1H, H-4eq) 4.524(dt, J=4Hz, 8.8Hz, 1H, H-2) 7.16-7.38(m, 10H, aromatic-CH).

Procedure A. Synthesis of methanesulfonic acid *Trans*-2-enzhydryl—tetrahydro-pyran-4-yl ester 4a

Methanesulfonyl chloride (0.62 g, 5.41 mmol) in dry methylene chloride (10 ml) was added dropwise to a mixture of *trans*-2-diphenylmethyl-4-hydroxy-pyran **3a** (0.73 g, 2.70 mmol), triethylamine (0.41 g, 4.06 mmol) in methylene chloride (10 ml) and was cooled to 0 °C. After one hour, the reaction was gradually allowed to reach room temperature over a period of four hours. Additional methylene chloride (20 ml) was added to the reaction mixture, and the mixture was washed in turn with saturated aqueous sodium bicarbonate, brine and water, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and purification by flash chromatography gave compound **4a** (0.93 g, 99.9% yield) as an oil.

^{1}H NMR (300mHz, $CDCl_3$): 1.54 (m, 1H, H-3ax) 1.82 (m, 1H, H-5ax) 1.95(m, 1H, H-3eq) 2.1(m,1H, H-5eq) 2.95(s, 3H, CH_3SO_2) 3.46(dt, 1H, H-6ax) 3.96(d, 1H, $(Ph)_2CH$) 4.1(m, 2H, H-2, H-6eq) 4.83(m, 1H, H-4) 7.15-7.38(m, 10H, aromatic-CH).

Synthesis of methanesulfonic acid *cis*-2-benzhydryl—tetrahydro-pyran-4-ylester 4b

cis-2-diphenylmethyl-4-hydroxy-pyran **3b** (0.3 g, 1.12 mmol) was reacted with methanesulfonyl chloride (0.26 g, 2.24 mmol) (Procedure A) to give compound **4b** (0.38 g, 98%) as an oil.

^{1}H NMR (300MHz, $CDCl_3$): 1.609(m, 1H, H-3ax) 1.8-1.96(m, 4H, -OH, H-3eq, H-5) 2.96(s, 3H, CH_3SO_2) 3.8-3.94(m, 3H, H-6, $(Ph)_2CH$) 4.46(dt, J=2Hz, 10Hz, 1H, H-2) 5.1(m, 1H, H-4) 7.16-7.38(m, 10H, aromatic-CH).

Procedure B. Synthesis of *cis*-4-azido-2-benzhydryl-tetrahydropyran (5a)

Into a solution of *trans*-2-diphenylmethylpyran-4-yl methanesulfonate **4a** (0.33 g, 0.95 mmol) in dry DMF (40 ml) was added sodium azide (0.18 g, 2.85 mmol). The mixture was heated to 100 °C and stirred for 4 hr. The mixture was diluted with ethyl ether, washed with 2M aqueous $NaHCO_3$ and brine, and then dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (Hexane/Ethyl Acetate 9:1) afforded compound **5a** (0.23 g, 82.7% yield) as a liquid.

^{1}H NMR (400MHz, $CDCl_3$) 1.5-1.68 (m, 3H, H-3, H-5eq) 1.855(m, 1H, H-5ax) 3.74-3.86(m, 2H, H-6) 3.87(d, J=9.2Hz, 1H, $(Ph)_2CH$) 4.02(m, 1H, H-4) 4.393(dt, J=3.2Hz, 13Hz, 1H, H-

2) 7.16-7.38(m, 10H, aromatic-CH).

Synthesis of *trans*-4-azido-2-benzhydryl-tetrahydropyran 5b

Cis-2-diphenylmethylpyran-4-yl methanesulfonate **4b** (0.38 g, 1.10 mmol) was reacted with sodium azide (0.29 g, 4.4 mmol) in dry DMF (Procedure B) to yield compound **5b** (0.26 g, 80%) as a liquid.

^{1}H NMR(500MHz, $CDCl_3$) 1.32(q, J=11Hz, 1H, H-3ax) 1.61(dq, J=5.5Hz, 13Hz, 1H, H-5ax) 1.82(m, 1H, H-3eq) 1.90(m, 1H, H-5eq) 3.44-3.50(m, 2H, H-4, H-6ax) 3.96(d, J=8.5Hz, 1H, $(Ph)_2CH$) 4.03(dt, J=2Hz, 9Hz, 1H, H-2) 4.08(ddd, J=2Hz, 5.5Hz, 12.5Hz, 1H, H-6eq) 7.16-7.38(m,10H, aromatic-CH).

Procedure C. Synthesis of *cis*-(2-benzhydryl-tetrahydropyran-4-yl)-amine (6a)

Cis-4-azido-2-diphenylmethyltetrahydropyran **5a** (0.23 g, 0.78 mmol) was hydrogenated (60 psi) in the presence of 10% Pd-C (0.02 g, 10%wt) for 4hr. Reaction mixture was filtered through a short bed of celite and removal of the solvent afforded 0.21 g (quantitative yield) product. This product was pure enough to continue to the next reaction step.

^{1}H NMR(300MHz, $CDCl_3$) 1.21-1.4(m, 4H, H-3, NH_2) 1.59(m, 1H, H-5ax) 1.87(m, 1H, H-5eq) 3.37(m, 1H, H-4) 3.77(m, 1H, H-6eq) 3.91(dt, J=2.4Hz, 11.7Hz, 1H, H-6ax) 3.94(d, J=9.3Hz, 1H, $(Ph)_2CH$) 4.56(dt, J=2.4Hz, 10.2Hz, 1H, H-2) 7.16-7.38(m, 10H, aromatic-CH)

Synthesis of *Trans*-(2-benzhydryl-tetrahydropyran-4-yl)-amine (6b)

Trans--4-azido-2-diphenylmethyltetrahydropyran **5b** (0.26 g, 0.89 mmol) was hydrogenated (Procedure C) to yield compound **6b** (0.24 g, quantitative).

^{1}H NMR(400MHz, $CDCl_3$) 1.15-1.25(m, 1H, H-3) 1.4-1.52(m, 1H, H-3) 1.7-1.88(m, 2H, H-5) 2.99(m, 1H, H-4) 3.41(dt, J=2Hz, 12.4Hz, 1H, H-6ax) 3.9-4.06(m, 3H, H-2, H-6ax, $(Ph)_2CH$) 4.7(bs, 2H, NH_2) 7.16-7.38(m, 10H, aromatic-CH)

Procedure D. Syntheis of *cis*-(2-benzhydryl-tetrahydropyran-4-yl)-(4-fluro-benzyl)-amine (7a)

Into a solution of *cis*-4-amino-2-diphenylmethyl pyran **6a** (0.2 g, 0.75 mmol), 4-flurobenzaldehyde (0.83 g, 0.67 mmol) and glacial acetic acid (0.45 g, 0.75 mmol) in 1,2-dichloroethane (20 ml) was added portion wise $NaCNBH_3$ (0.57 g, 0.9 mmol) dissolved in methanol (5 ml). After 4hr, water was added to quench the reaction and the mixture was stirred for 30 minutes at 0 ^{0}C. Then the mixture was basified with saturated aqueous $NaHCO_3$ and extracted thrice with methylene chloride (3 x 30 ml). The combined organic

phase was washed with brine, water and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo to collect the crude residue. The residue was purified by flash chromatography (Hexane/Ethyl Acetate/Triethylamine 3:2:0.2) to give *cis*-2-diphenylmethyl-4-(4-flurobenzylamino)-tetrahydropyran **7a** (0.20 g, 72.6%) as a liquid.
^{1}H NMR (400MHz, $CDCl_3$) 1.24(bs, 1H, -NH) 1.28(m, 1H, H-3) 1.45-1.58(m, 2H, H-3, H-5eq) 1.83(tt, J=4Hz, 13Hz, 1H, H-5ax) 3.07(m, 1H, H-4) 3.65(s, 2H, (F)Ph-CH_2) 3.75(m, 1H, H-6eq) 3.91(d, J=9.6Hz, 1H, $(Ph)_2CH$) 3.94(dt, J=2.4Hz, 12Hz, 1H, H-6ax) 4.59(dt, J=3.2Hz, 9.6Hz, 1H, H-2) 6.9-7.4(m, 14H, aromatic-CH).
Free base was converted into its oxalate salt: mp 177-181 ^{0}C, Anal. [$C_{25}H_{26}NOF \cdot (COOH)_2$] C, H, N.

Synthesis of *trans*-(2-benzhydryl-tetrahydropyran-4-yl)-(4-fluro-benzyl)-amine 7b,

trans-4-Amino-2-diphenylmethyl pyran **6b** (0.24 g, 0.90 mmol) was reacted with 4-fluorobenzaldehyde (0.11 g, 0.90 mmol) in presence of acetic acid (0.05 g, 0.9 mmol), and then reduced with $NaCNBH_3$ (0.07 g, 1.08 mmol) to yield compound **7b** (0.18 g, 54%) (Procedure D).
^{1}H NMR(500MHz, $CDCl_3$) 1.13(q, J=10.5Hz, 1H, H-3ax) 1.32(broad, NH) 1.38(dq, J=5Hz, 12.5Hz, 1H, H-5ax) 1.74(m, 1H, H-3eq) 1.87(m, 1H, H-5eq) 2.722(tt, J=4Hz, 11.5Hz, 1H, H-4) 3.444(dt, J=2Hz, 12Hz, 1H, H-6ax) 3.683(d, J=13.5Hz, 1H, (F)Ph-CH) 3.754(d, J=13Hz, 1H, (F)Ph-CH) 3.936(d, J=9Hz, 1H, $(Ph)_2CH$) 4.0-4.08(m, 2H, H-2, H-6eq) 6.9-7.38(m, 14H, aromatic-CH).
Free base was converted into its oxalate salt: mp 185-187 C Anal. [$C_{25}H_{26}NOF \cdot (COOH)_2$] C, H, N.

Synthesis of 1,1-diphenyl-hex-5-en-2-ol (8)

A dry three-neck, round-bottom flask fitted with a reflux condensor, air-balance drop funnel and nitrogen inlet was charged with Mg (0.11 g, 4.44 mmol) and a crystal of I_2. The flask was warmed (heat gun) to volatilize the I_2 under vacuum, and then was allowed to cool. Dry ethyl ether (10 ml) was added next followed by introduction of catalytic neat 4-bromo-1-butene (0.02 g). The reaction was initiated by brief warming and then the rest of total amount of bromide (0.4 g, 2.96 mmol) in dry ethyl ether (5 ml) was added dropwise over 5 minutes. The mixture was refluxed for 30 minutes and then was allowed to reach 0□C. Into the stirred Grignard reagent solution was added dropwise a solution of diphenylacetaldehyde **1** (0.64 g, 3.26 mmol) in dry ethyl ether (5 ml), and the reaction mixture was stirred for an additional 3.5 hr at room temperature. Saturated aqueous $NaHCO_3$ was added to the reaction mixture at 0 °C, organic phase was separated and the

aqueous phase was extracted thrice with ethyl ether (3 x 20 ml). Combined organic phase was washed with brine and water, then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and flash chromatography of the crude residue (SiO2, hexane/Ethyl Acetate 9:1) gave 1,1-diphenyl-hex-5-en-2-ol **8** (0.68 g, 91%) as a liquid. ^{1}H NMR(400MHz, $CDCl_3$) 1.45-1.70(m, 2H, H-3) 1.69(bd, -OH) 2.1-2.4(m, 2H, H-4) 3.91(d, J=8.4 Hz, 1H, H-1) 4.39(m, 1H, H-2) 4.95-5.1(m, 2H, H-6) 5.81(m, 1H, H-5) 7.16-7.38(m, 10H, aromatic-CH)

Synthesis of 1,1-diphenyl-2-(1-ethenoxy)-hex-5-ene (9)

Into a mixture of 1,1-diphenyl-hex-5-en-2-ol **2** (7 g, 27.78 mmol) in ethyl vinyl ether (250 ml) was added $Hg(OCOCF_3)_2$ (2.37 g, 5.56 mmol) and was stirred overnight at room temperature. The reaction mixture was neutralized by addition of sat. aqueous $NaHCO_3$. Organic phase was separated and the aqueous layer was extracted with ethyl ether, dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (Hexane/Ethyl Acetate 20:1) gave 1,1-diphenyl-2-(1-ethenoxy)-hex-5-ene **9** (5.1 g, 66%) as a liquid. ^{1}H NMR(400MHz, $CDCl_3$) 1.58-1.78(m, 2H, H-3) 2.08-2.30(m, 2H, H-4) 3.86(dd, J=1.6Hz, 8.4Hz, 1H, H-2') 4.15(d, J=8Hz, 1H, Ph_2CH) 4.25(dd, J=1.6Hz, 14Hz, 1H, H-2') 4.50(m, 1H, H-2) 5.00(m, 2H, H-6) 5.77(m, 1H, H-5) 6.15(dd, J=6.8Hz, 14.8Hz, 1H, H-1') 7.16-7.38(m, 10H, aromatic-CH)

Synthesis of 2-benzhydryl-3,4-dihydro-2H-pyran (10)

A solution of 1,1-diphenyl-2-(1-ethenoxy)-hex-5-ene **9** (5.1 g, 18.3 mmol) and Grubb's catalyst (1.5 g, 1.83 mmol) in benzene (200 ml) was heated under reflux for 20 hr. The solvent was removed under vacuo and the residue was chromatographed over silica gel (Hexane/Ethyl Acetate 20:1) to give 2-diphenyl-3,4-dihydro-2H-pyran **10** (4.25 g, 92.6%) as a liquid.

^{1}H NMR(400MHz, $CDCl_3$) 1.52-1.66(m, 1H, H-3) 1.76-1.84(m, 1H, H-3) 1.92-2.14(m, 2H, H-4) 4.08(d, J=9.2Hz, 1H, Ph_2CH) 4.59(dt, J=2.4Hz, 8.8Hz, 1H, H-2) 4.72(m, 1H, H-5) 6.38(d, J=6.4Hz, 1H, H-6) 7.16-7.50(m, 10H, aromatic-CH).

Synthesis of *Trans*-6-benzhydryl-tetrahydropyran-3-ol (11)

Into a solution of 0.5M 9-BBN-THF complex (24 ml, 12 mmol) in dry THF (20 ml) was added in a drop wise manner 2-diphenyl-3,4-dihydro-2H-pyran **10** (1 g, 4 mmol) dissolved in dry THF(10 ml). The mixture was kept under stirring at room temperature. After the completion of initial addition reaction , the intermediate reaction mixture was oxidized with 5.3 ml 3N sodium hydroxide and 3 ml of 30% hydrogen peroxide. The reaction was continued at 55 °C for 1 hr to insure the completion of oxidation. After the

mixture was diluted with sat. aqueous $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 X 40 ml). The combined extract was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash chromatography (Hexane/Ethyl Acetate 7:3) to furnish *trans*-6-diphenyltetrahydropyran-3-ol **11** (1 g, 93.5%) as a liquid.

^1H NMR(300MHz, $CDCl_3$) 1.32-1.44(m, 2H, H-5) 1.54-1.64(m, 1H, H-4) 1.75(bs, 1H, OH) 2.02-2.14(m, 1H, H-4) 3.14(t, J=10.2Hz, 1H, H-2ax) 3.67(m, 1H, H-3) 3.90(d, J=9.3Hz, 1H, Ph_2CH) 3.95-4.04(m, 2H, H-2eq, H-6) 7.16-7.38(m, 10H, aromatic-CH).

Synthesis of 6-benzhydryl-dihydro-pyran-3-one (12)

Into a solution of DMSO (0.13 g, 1.64 mmol) in methylene chloride (5 ml) at –78 °C was added a solution of oxalyl chloride (0.11 g, 0.82 mmol) in methylene chloride (1 ml) in a drop wise manner. A solution of *trans*-2-diphenylmethyl-tetrahydropyran-5-ol **11** (0.2 g, 0.75 mmol) in methylene chloride (2 ml) was added next. The reaction was continued for 15 minutes, triethylamine (0.38 g, 3.73 mmol) was next added portion wise and the reaction mixture was allowed to come to room temperature for over a period of 30 minutes. Additional methylene chloride (10 ml) was added, and washed with sat. aqueous $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (SiO2, Hexane/Ethyl Acetate 8.5:1.5) gave 2-diphenylmethyl-dihydro-pyran-5-one **12** (0.18 g, 91%) as a liquid.

^1H NMR(300MHz, $CDCl_3$) 1.9-1.98(m, 2H, H-5) 2.38-2.62(m, 2H, H-4) 4.0(d, J=17.1Hz, 1H, H-2) 4.05(d, J=9Hz, 1H, Ph_2CH) 4.17(dd, J=1.8Hz, 16.2Hz, 1H, H-2) 4.44(dt, J=5.2Hz, 8.4Hz, 1H, H-6) 7.16-7.38(m, 10H, aromatic-CH).

^{13}C NMR(75MHz, $CDCl_3$) δ (ppm) 21.50, 32.00, 55.72, 65.62, 76.05, 126.89, 127.09, 128.60, 128.68, 128.90, 128.97, 141.36, 141.62, 146.77.

Synthesis of *Trans*-(6-benzhydryl-tetrahydropyran-3-yl)-(34-flurobenzy)-amine (16a)

2-diphenylmethyl-dihydro-pyran-5-one **12** (0.18 g, 0.68 mmol) was reacted with 4-flurobenzylamine (0.08 g, 0.68 mmol) in the presence of glacial acetic acid (0.041 g, 0.68 mmol) in 1,2-dichloroethane (10 ml) at room temperature, and then reduced by $NaCNBH_3$ (0.051 g, 0.81 mmol) (Procedure D) to yield a mixture of **16a** and **16b**. *cis*-2-Diphenylmethyl-5-(4-flurobenzylamino)-tetrahydropyran **16b** was eluted first (0.04 g, 15%).

^1H NMR(300MHz, $CDCl_3$) 1.33(m, 1H, H-5) 1.46-1.72(m, 2H, H-5, H-4) 1.935(m, 1H, H-4) 2.031(bm, 1H, NH) 2.641(m, 1H, H-3) 3.571(dd, J=1.8Hz, 11.4Hz, 1H, H-2ax) 3.75(m, 2H, (F)Ph-CH_2) 3.95-4.14(m, 3H, H-6, H-2eq, Ph_2CH) 6.9-7.38(m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 229-230 ^{0}C Anal. [$C_{25}H_{26}NOF$, $(COOH)_2$] C, H, N.

Eluted second was *trans*-2-diphenylmethyl-5-(4-flurobenzylamino)-tetrahydropyran **16a** (0.11 g, 45%).

^{1}H NMR(300MHz, $CDCl_3$) 1.24-1.44(m, 2H, H-5) 1.55(m, 1H, H-4) 1.748(bm, NH) 2.02(m, 1H, H-4) 2.68(m, 1H, H-3) 3.11(t, J=10.8Hz, 1H, H-2ax) 3.76(s, 2H, (F)-Ph-CH_2) 3.89(d, J=9Hz, 1H, Ph_2CH) 3.99(dt, J=3Hz, 8.7Hz, 1H, H-6) 4.08(m, 1H, H-2eq) 6.9-7.38(m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 141-143 ^{0}C Anal. [$C_{25}H_{26}NOF$, $(COOH)_2$ $0.65H_2O$] C, H, N.

Synthesis of methanesulfonic acid *trans*-6-benzhydryl-tetra-hydropyran-3-yl ester (13)

Methanesulfonyl chloride (0.33 g, 2.87 mmol) was reacted with *trans*-2-diphenylmethyl-tetrahydropyran-5-ol **11** (0.38 g, 1.43 mmol) in the presence of triethylamine (0.22 g, 2.15 mmol) in methylene chloride (10 ml) to give *trans*-2-diphenylmethyl tetrahydropyran-5-yl methanesulfonate **13** (0.39 g, 77.8%) as an oil (Procedure A).

^{1}H NMR(400MHz, $CDCl_3$) 1.47(m, 1H, H-5) 1.62-1.78(m, 2H, H-5, H-4) 2.25(m, 1H, H-4) 2.96(s, 3H, CH_3SO_2) 3.36(t, J=10.4Hz, 1H, H-2ax) 3.89(d, J=8.8Hz, 1H, Ph2CH) 4.00(dt, J=2Hz, 9.6Hz, 1H, H-6) 4.14(m, 1H, H-2eq) 4.61(m, 1H, H-3) 7.16-7.38(m, 10H, aromatic-CH).

Synthesis of *Cis*-3-azido-6-benzhydryl-tetrahydropyran (14)

trans-2-Diphenylmethyl-tetrahydropyran-5-yl methanesulfonate **13** (0.39 g, 1.12 mmol) in dry DMF (50 ml) was reacted with sodium azide (0.22 g, 3.35 mmol) to yield *cis*-5-azido-2-diphenylmethyl-tetrahydropyran **14** (0.3 g, 92%) as an oil (Procedure B).

^{1}H NMR (300MHz, $CDCl_3$) 1.36 (m, 1H, H-5) 1.54-1.85 (m, 2H, H-5, H-4) 1.98 (m, 1H, H-4), 3.55 (m, 1H, H-3), 3.64 (dd, J=1.8Hz, 12.6Hz, 1H, H-2) 3.95-4.15(m, 3H, H-2, H-6, Ph_2CH) 7.16-7.38(m, 10H, aromatic-CH)

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-amine (15)

Cis-5-azido-2-diphenylmethyl-tetrahydropyran **14** (0.3 g, 1.02 mmol) in methanol (25 ml) was hydrogenated under the catalyst of 10% Pd-C (0.03 g, 10% wt) for 4 hr (Procedure C) to give *cis*-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.21 g, 78%) as an oil.

^{1}H NMR(400MHz, CD_3OD) 1.31(m, 1H, H-5eq) 1.54(m, 1H, H-5ax) 1.70-1.86(m, 2H, H-4)

2.90(bs, bs, 1H, H-3) 3.68(m, 2H, H-2) 3.96(d, J=9.2Hz, 1H, Ph_2CH) 4.13(dt, J=2Hz, 9.6Hz, 1H, H-6) 7.10-7.40(m, 10H, aromatic-CH). Free base was converted to HCl salt: mp 260-261 °C Anal. [$C_{18}H_{21}NO \cdot$ HCl $0.2H_2O$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-fluoro-benzyl)-amine (16b)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.21 g, 0.79 mmol) was reacted with 4-flurobenzaldehyde (0.098 g, 0.79 mmol) in the presence of glacial acetic acid(0.047 g, 0.79 mmol) in 1,2-dichloroethane (20 ml), and then reduced by $NaCNBH_3$ (0.059 g, 0.95 mmol) in methanol (5 ml) (Procedure D) to give compound **16b** (0.24 g, 82%).

^{1}H NMR(300MHz, $CDCl_3$) 1.33(m, 1H, H-5) 1.46-1.72(m, 2H, H-5, H-4) 1.935(m, 1H, H-4) 2.031(bm, 1H, NH) 2.641(m, 1H, H-3) 3.571(dd, J=1.8Hz, 11.4Hz, 1H, H-2ax) 3.75(m, 2H, (F)Ph-CH_2) 3.95-4.14(m, 3H, H-6, H-2eq, Ph_2CH) 6.9-7.38(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 229-230 °C Anal. [$C_{25}H_{26}NOF \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-cyano-benzyl)-amine (16c)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.15 g, 0.56 mmol) was reacted with 4-cyanobenzaldehyde (0.07 g, 0.56 mmol) in the presence of glacial acetic acid(0.033 g, 0.56 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.042 g, 0.67 mmol) in methanol (5 ml) (Procedure D) to give compound **16c** (0.17 g, 80%) as an oil. ^{1}H NMR (300MHz, $CDCl_3$) 1.36(m, 1H, H-5) 1.46-1.58(m, 1H, H-5) 1.58-1.74(m, 1H, H-4) 1.931(m, 1H, H-4) 2.615(bm, 1H, H-3) 3.59(dd, J=1.8Hz, 11.7Hz, H-2ax) 3.83(m, 2H, (CN)Ph-CH_2) 3.95-4.16(m, 3H, H-6, H-2eq, Ph_2CH) 7.16-7.62(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 241-242 °C Anal. [$C_{26}H_{26}N_2O \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-nitro-benzyl)-amine (16d)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.1g, 0.38 mmol) was reacted with 4-nitrobenzaldehyde (0.057 g, 0.38 mmol) in the presence of glacial acetic acid (0.023 g, 0.38 mmol) in 1,2-dichloroethane (20 ml), and then reduced by $NaCNBH_3$ (0.03 g, 0.45 mmol) in methanol (5 ml) (Procedure D) to give compound **16d** (0.12 g, 80%) as an oil. ^{1}H NMR (300MHz, $CDCl_3$) 1.35(m, 1H, H-5) 1.53(m, 1H, H-5) 1.67(tt, J=3.6Hz, 13.5Hz, 1H, H-4) 1.91(m, 2H, H-4, NH) 2.62(m, 1H, H-3) 3.58(dd, J=1.8Hz, 9.6Hz, 1H, H-2ax) 3.87(m, 2H, (NO_2)Ph-CH_2) 3.92-4.14(m, 3H, H-6, H-2eq, Ph_2CH) 7.14-7.54, 8.12-8.2(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 236-238 °C Anal. [$C_{25}H_{26}N_2O_3 \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-methoxy-benzyl)-amine

(16e)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.15 g, 0.56 mmol) was reacted with 4-methoxybenzaldehyde (0.078 g, 0.56 mmol) in the presence of glacial acetic acid (0.033 g, 0.56 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.042 g, 0.67 mmol) in methanol (5 ml) (Procedure D) to give compound **16e** (0.17 g, 78%) as an oil.

^1H NMR (300MHz, $CDCl_3$) 1.35(m, 1H, H-5) 1.48-1.76(m, 2H, H-5, H-4) 1.88-2.02(m, 1H, H-4) 2.68(bs, 1H, H-3) 3.59(dd, J=12.3Hz, 2.4Hz, 1H, H-2ax) 3.76(d, J=7.2Hz, 2H, $(CH_3O)Ph-CH_2$) 3.825(s, 3H, CH_3O-3.98-4.16(m, 3H, H-6, H-2eq, Ph_2CH) 6.88-6.94, 7.18-7.44(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 215-217 ^{0}C Anal. [$C_{26}H_{29}NO_2 \bullet (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(3-indole-methyl)-amine (16f)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.12g, 0.45 mmol) was reacted with 3-indole-carboxaldehyde (0.065 g, 0.45 mmol) in the presence of glacial acetic acid (0.027 g, 0.45 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.034 g, 0.54 mmol) in methanol (5 ml) (Procedure D) to give compound **16f** (0.15 g, 82%) as an oil.

^1H NMR (400MHz, $CDCl_3$) 1.34(m, 1H, H-5) 1.53(m, 1H, H-5) 1.67(tt, J=14Hz, 4Hz, 1H, H-4) 1.93(m, 1H, H-4) 2.37(bm, 1H, NH) 2.65(bs, 1H, H-3) 3.57(dd, J=10.7Hz, 1.6Hz, 1H, H-2ax) 3.96(s, 2H, 2-Indole-CH_2) 3.92-4.14(m, 3H, H-6, H-2eq, Ph_2CH) 6.35(s, 1H, Indole-3-H) 7.05-7.6(m, 14H, aromatic-CH) 9.1(s, 1H, Indole-NH). Free base was converted into oxalate: mp 177-179 ^{0}C Anal. [$C_{27}H_{28}N_2O$ □ $(COOH)_2$ $0.5H_2O$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(2-indole-methyl)-amine (16g)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.067 g, 0.25 mmol) was reacted with 2-indole-carboxaldehyde (0.036 g, 0.25 mmol) in the presence of glacial acetic acid (0.015 g, 0.25 mmol) in 1,2-dichloroethane (20 ml), and then reduced by $NaCNBH_3$ (0.019 g, 0.3 mmol) in methanol (5 ml) (Procedure D) to give compound**16g** (0.081 g, 82%) as an oil.

^1H NMR (300MHz, $CDCl_3$) 1.33(m, 1H, H-5) 1.48-1.76(m, 2H, H-5, H-4) 1.99(m, 1H, H-4) 2.27(bs, 1H, NH) 2.79(m, 1H, H-3) 3.6(dd, J=1.8Hz, 12.3Hz, 1H, H-2ax) 3.998(s, 2H, Indole-3-CH_2) 4.02-4.2(m, 3H, H-6, H-2eq, Ph_2CH) 7.0-7.8(m, 14H, aromatic-CH) 8.42(s, 1H, Indole-NH). Free base was converted into oxalate: mp 215-216 ^{0}C Anal. [$C_{27}H_{28}N_2O \bullet (COOH)_2$ $0.5H_2O$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-hydroxy-benzyl)-amine (16h)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.15 g, 0.56 mmol) was reacted with 4-hydroxybenzaldehyde (0.067 g, 0.56 mmol) in the presence of glacial acetic acid (0.034 g, 0.56 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.042 g, 0.67 mmol) in methanol (5 ml) (Procedure D) to give compound **16h** (0.17 g, 80%) as an oil. ^1H NMR (400MHz, $CDCl_3$) 1.34(m, 1H, H-5) 1.50(m, 1H, H-5) 1.67(tt, J=4Hz, 13.6Hz, 1H, H-4) 2.02(m, 1H, H-4) 2.71(m, 1H, H-3) 3.56(dd, J=1.6Hz, 11.6Hz, 1H, H-2ax) 3.64(m, 2H, (HO)Ph-CH_2) 3.95(d, J=8.0Hz, 1H, Ph_2CH) 4.02-4.14(m, 2H, H-6, H-2eq) 6.52(m, 2H, aromatic-CH) 6.9-7.38(m, 12H, aromatic-CH). Free base was converted into oxalate: mp 136-138 ^{0}C Anal. [$C_{25}H_{27}NO_2 \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(3,4-dichloro-benzyl)-amine (16i)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.1g, 0.38 mmol) was reacted with 3,4-dichlorobenzaldehyde (0.066 g, 0.38 mmol) in the presence of glacial acetic acid(0.023 g, 0.38 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.03 g, 0.45 mmol) in methanol (5 ml) (Procedure D) to give compound **16i** (0.12 g, 75%) as an oil. ^1H NMR (500MHz, $CDCl_3$) 1.34(m, 1H, H-5) 1.52(m, 1H, H-5) 1.66(m, 1H, H-4) 1.79(bs, 1H, NH) 1.91(m, 1H, H-4) 2.61(m, 1H, H-3) 3.57(dd, J=1.5Hz, 11.5Hz, 1H, H-2ax) 3.72(m, 2H, (Cl,Cl)Ph-CH_2) 3.94-4.05(m, 2H, H-2eq, Ph_2CH) 4.08(dt, J=2Hz, 8.5Hz, 1H, H-6) 7.1-7.5(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 251-252 ^{0}C Anal. [$C_{25}H_{25}NOCl_2 \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(3,4-difluoro-benzyl)-amine (16j)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.1 g, 0.38 mmol) was reacted with 3,4-difluorobenzaldehyde (0.055 g, 0.38 mmol) in the presence of glacial acetic acid (0.023 g, 0.38 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.03 g, 0.45 mmol) in methanol (5 ml) (Procedure D) to give compound **16j** (0.12 g, 80%). ^1H NMR (300MHz, $CDCl_3$) 1.34(m, 1H, H-5) 1.52(m, 1H, H-5) 1.66(tt, J=3.6Hz, 13.5Hz, 1H, H-4) 1.76(bs, 1H, NH) 1.92(m, 1H, H-4) 2.61(m, 1H, H-3) 3.57(dd, J=1.8Hz, 11.4Hz, 1H, H-2ax) 3.72(m, 2H, (F,F)Ph-CH_2) 3.94-4.14(m, 3H, H-6, H-2eq, Ph_2CH) 6.9-7.38(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 234-235 ^{0}C Anal. [$C_{25}H_{25}NOF_2 \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-benzyl-amine (16k)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.03 g, 0.11 mmol) was reacted with benzaldehyde (0.012 g, 0.11 mmol) in the presence of glacial acetic acid

(0.007 g, 0.11 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.009 g, 0.14 mmol) in methanol (5 ml) (Procedure D) to give compound **16k** (0.034 g, 85%).

^1H NMR (300MHz, $CDCl_3$) 1.30(m, 1H, H-5) 1.44-1.70(m, 2H, H-5, H-4) 1.80(bs, 1H, NH) 1.92(m, 1H, H-4) 2.64(m, 1H, H-3) 3.55(dd, J=1.8Hz, 11.7Hz, 1H, H-2ax) 3.77(m, 2H, Ph-CH_2) 3.92-4.1(m, 3H, Ph_2CH, H-6, H-2eq) 7.0-7.38(m, 15H, aromatic-CH). Free base was converted into oxalate: mp 208-210 ^{0}C Anal. [$C_{25}H_{27}NO \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-bromo-benzyl)-amine (16l)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.04 g, 0.15 mmol) was reacted with 4-bromobenzaldehyde (0.028 g, 0.15 mmol) in the presence of glacial acetic acid(0.009 g, 0.15 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.012 g, 0.18 mmol) in methanol (5 ml) (Procedure D) to give compound **16l** (0.052 g, 80%) as an oil.

^1H NMR (400MHz, $CDCl_3$) 1.31(m, 1H, H-5) 1.50(m, 1H, H-5) 1.64(m, 1H, H-4) 1.80(bs, 1H, NH) 1.90(m, 1H, H-4) 2.61(m, 1H, H-3) 3.56(dd, J=1.6Hz, 11.6Hz, 1H, H-2ax) 3.72(m, 2H, (Br)-Ph-CH_2) 3.94-4.30(m, 2H, Ph_2CH, H-2eq) 4.07(dt, J=1.6Hz, J=9.6Hz, 1H, H-6) 7.0-7.42(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 250-252 ^{0}C Anal. [$C_{25}H_{26}BrNO \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-iodo-benzyl)-amine (16m)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.04 g, 0.15 mmol) was reacted with 4-iodobenzaldehyde (0.045 g, 0.15 mmol) in the presence of glacial acetic acid (0.009 g, 0.15 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.012 g, 0.18 mmol) in methanol (5 ml) (Procedure D) to give compound **16m** (0.059 g, 81%) as an oil.

^1H NMR (400MHz, $CDCl_3$) 1.28(m, 1H, H-5) 1.50(m, 1H, H-5) 1.64(m, 1H, H-4) 1.72(bs, 1H, NH) 1.90(m, 1H, H-4) 2.60(m, 1H, H-3) 3.56(dd, J=1.6Hz, 12.4Hz, 1H, H-2ax) 3.71(m, 2H, (I)-Ph-CH_2) 3.92-4.02(m, 2H, Ph_2CH, H-2eq) 4.06(dt, J=1.6Hz, J=9.2Hz, 1H, H-6) 7.0-7.70(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 243-244 ^{0}C Anal. [$C_{25}H_{26}INO \cdot (COOH)_2$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(1H-iodo-5-ylmethyl)-amine (16n)

Trans-5-amino-2-diphenylmethyl-tetrahydropyran **15** (0.05 g, 0.19 mmol) was reacted with 5-indole-carboxaldehyde (0.027 g, 0.19 mmol) in the presence of glacial acetic acid(0.011 g, 0.19 mmol) in 1,2-dichloroethane (20 ml), and $NaCNBH_3$ (0.024 g, 0.37 mmol) in methanol (5 ml) (Procedure D) to give compound **16n** (0.061 g, 82%) as an oil.

^1H NMR (400MHz, $CDCl_3$) 1.32(m, 1H, H-5) 1.50-1.70(m, 2H, H-5, H-4) 1.95(m, 2H, H-4,

NH) 2.71(bs, 1H, H-3) 3.57(dd, J=2Hz, 12Hz, 1H, H-2ax) 3.88(m, 2H, Indole-CH_2) 3.96-4.12(m, 3H, Ph_2CH, H-2eq, H-6) 6.51, 7.1-7.4, 7.57(m, 15H, aromatic-CH) 8.36(bs, 1H, NH). Free base was converted into oxalate: mp 128-130 ^{0}C Anal. [$C_{27}H_{28}N_2O \cdot (COOH)_2$ $0.5H_2O$] C, H, N.

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-amino-benzyl)-amine (16o)

A mixture of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-nitro-benzyl)-amine (**16f**) (0.16 g, 0.39 mmol) and $SnCl_2/2H_2O$ (0.35 g, 1.55 mmol) in EtOH/EtOAc (20 ml, 7:3) was heated to reflux for 1.5h (monitored by TLC, Hex/EtOAc/Et_3N 5:5:0.4). After removal of the solvent, the residue was diluted with 10% NaHCO3 and EtOAc and stirred vigorously for 30 min. After filtration the organic phase was separated and the aqueous phase was extracted with EtOAc (20 ml x 2). The combined organic phase was dried over Na_2SO_4. After removal of the solvent, flash chromatography gave **16o**, *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-amino-benzyl)-amine (0.087 g, 60%).

^{1}H NMR (400MHz, $CDCl_3$) 1.3(m, 1H, H-5) 1.47(m, 1H, H-5) 1.64(tt, J=4Hz, 12.8Hz, 1H, H-4) 1.90(m, 1H, H-4) 2.53-2.70(m, 3H, H-3, (NH_2)-$PhCH_2$) 3.54(dd, J=1.6 Hz, 11.2Hz, 1H, H-2ax) 3.92-4.0(m, 2H, Ph_2CH, H-2eq) 4.06(dt, J=2.4Hz, 9.6Hz, 1H, H-6) 7.06-7.38(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 151-153 ^{0}C Anal. [$C_{25}H_{28}N_2O \cdot 2(COOH)_2$ $0.3H_2O$] C, H, N.

Synthesis of *Cis*-N-(6-benzhydryl-tetrahydro-pyran-3-yl)-2-(4-fluoro-phenyl)-acetamide (17)

Into a solution of 4-fluorophenylacetic acid (0.23 g, 1.46 mmol) in dichloromethane (25 ml) was added oxalyl chloride (0.22 g, 1.76 mmol) dissolved in dichloromethane (5 ml) at 0°C which was followed by addition of one drop of DMF. The reaction mixture was allowed to reach at room temperature over a period of 2 hours. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane (5 ml) and was added into a solution of *cis*-N-(6-benzhydryl-tetrahydropyran-3-yl)-amine (0.26 g, 0.96 mmol) and triethylamine (0.31 g, 1.46 mmol) in dichloromethane (25 ml) at 0°C. After 20 minutes the reaction mixture was allowed to come to room temperature. After 3 hours, more dichloromethane was added and the mixture was washed in turn with 1N $NaHCO_3$, H_2O and brine, then dried over anhydrous Na_2SO_4. The solvent was removed under *vacuo*, and the residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to give *cis*-N-(6-benzhydryl-tetrahydropyran-3-yl)-2-(4-fluorophenyl)-acetamide **17** (0.31 g, yield 80%) as an oil.

^{1}H NMR (300MHz, $CDCl_3$) 1.1-1.4(m, 2H, H-5) 1.6-1.93(m, 2H, H-4) 3.49(s, 2H, Ph-CH_2CO) 3.63(dd, J=1.8Hz, 11.7Hz, 1H, H-2ax) 3.7-3.85(m, 2H, Ph_2CH, H-3) 3.9-4.08(m, 2H, H-6, H-2eq) 6.9-7.4(m, 14H, aromatic-CH).

Synthesis of *Cis*-(6-benzhydryl-tetrahydropyran-3yl)-[2-(4-fluoro-phenyl)-ethyl]-amine (16p)

Into a suspension of $NaBH_4$ (0.21 g, 3.33 mmol) in dry THF (20 ml) was added $BF_3{\cdot}Et_2O$ drop wise at 0°C. The mixture was stirred for 1.5 Hours at room temperature and cooled to 0°C. A solution of *cis*-N-(6-benzhydryl-tetrahydropyran-3-yl)-2-(4-fluorophenyl)-acetamide (0.17 g, 0.42 mmol) in dry THF (10 ml) was added drop wise into the solution. The mixture was refluxed overnight and cooled to room temperature. Methanol was added to quench the reaction followed by removal of solvent in vacuo. Into the residue was added 20 ml 10% HCl/MeOH and refluxed for 1 hour. The reaction mixture was cooled down to room temperature and solid $NaHCO_3$ was added at 0°C to pH9. The aqueous phase was extracted with dichloromethane (3 x 20 ml). The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo*. Flash chromatography gave **16p** *Cis*-(6-benzhydryl-tetrahydropyran-3yl)-[2-(4-fluoro-phenyl)-ehtyl]-amine (0.13 g, yield 81%).

^{1}H NMR (300MHz, $CDCl_3$) 1.2-1.42(m, 2H, H-5, NH) 1.61(m, 1H, H-5) 1.88(m, 2H, H-4) 2.64(m, 1H, H-3) 2.72-2.82(m, 4H, Ph-CH_2CH_2) 3.55(dd, J=1.8Hz, 11.7Hz, 1H, H-2ax) 3.86-3.98(m, 2H, Ph_2CH, H-2eq) 4.03(dt, J=3Hz, 10Hz, 1H, H-6) 6.9-7.4(m, 14H, aromatic-CH). Free base was converted into oxalate: mp 240-242 °C Anal. [$C_{26}H_{28}NOF \cdot (COOH)_2$] C, H, N.

Biology. The affinity of test compounds in binding to rat DAT, SERT, and NET was assessed by measuring inhibition of binding of 5.0 nM [^{3}H]WIN 35,428, 3.5 nM [^{3}H]citalopram, and 1.1 nM [^{3}H]nisoxetine, respectively, exactly as described by us previously. Briefly, rat striatum was the source for DAT, and cerebral cortex for SERT and NET. Final [Na^+] was 30 mM for DAT and SERT assays, and 152 nM for NET assays. All binding assays were conducted at 0-4°C, for a period of 2h for [^{3}H]WIN 35,428 and [^{3}H]citalopram binding, and 3h for [^{3}H]nisoxetine binding. Nonspecific binding of [^{3}H]WIN 35,428 and [^{3}H]citalopram binding was defined with 100uM cocaine, and that of [^{3}H]nisoxetine binding with 1 uM desipramine. Radioligand Kd values were 2.1, 3.2 and 2.2 nM, respectively. Test compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted out in 10% (v/v) DMSO. Additions from the latter stocks resulted in a final

concentration of DMSO of 0.5%, which by itself did not interfere with radioligand binding. At lease five triplicate concentrations of each test compound were studied, spaced evenly around the IC50 value. For DAT uptake assays, uptake of 50 nM [^{3}H]DA into rat striatal synaptosomes was measured exactly as described by us previously. Briefly, rat striatal P_2 membrane fractions were incubated with test compounds for 8min followed by the additional presence of [^{3}H]DA for 4min at 25°C. Nonspecific uptake was defined with 100uM cocaine. Construction of inhibition curves and dissolvement of test compounds were as described above.

References:

(1) (a) Substance Abuse and Mental Health Services Administration National Household Survey on Drug Abuse: Main Findings **1997**; Department of Health and Human Services: Washington, DC, **1998**. (b) Mathias, R. Cocaine, marijuana and heroin abuse up, methamphetamine abuse down. NIDA Notes **2000**, 15 (3), 4-5.

(2) Johanson, C. E.; Fischman, M. W. The Pharmacology of Cocaine Related to its Abuse. Pharmacol. Rev. **1989**, *41* (1), 3-52.

(3) Carroll, F. I.; Howell, L. L.; Kuhar, M. J. Pharmacotherapies for Treatment of Cocaine Abuse: Preclinical Aspects. *J. Med. Chem.* **1999**, *42*, 2721-2736.

(4) Ritz, M. C.; Cone, E. J.; Kuhar, M. J. Cocaine inhibition of ligand binding at dopamine , norpinephrine and serotonin transporters: A structure-activity study. *Life Sci.* **1990**, *46*, 635-645.

(5) Ritz, M.C.; Lamb, R. J.; Goldberg, R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-adminstration of cocaine. *Science*. **1987**, *237*, 1219-1223.

(6) Robinson, T.; Barridge, K. C. The neural basis of drug craving: An incentive-sensitization theory of addiction. Brain. Res. Rev. **1993**, *18*, 249-291.

(7) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing properties of cocaine. Trends. Neurosci. **1991**, *14*, 299-302.

(8) Giros, B., Jaber, M., Jones, S. R., Wightman, R. M., Caron, M. G. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature. **1996,** 379, 606-612.

(9) Spealman, R. D., Madras, B. K., Bergman, J. Effects of Cocaine and Related Drugs in

Nonhuman Primates. II. Stimulant Effects on Schedule-Controlled Behavior. Pharmacol. Exp. Ther. **1989,** 251, 142-149.

(10) Witkin, J. M., Nichols, D. E., Terry, P., Katz, J. L. Behavioral effects of selective dopaminergic compounds in rats discriminating cocaine injections. J. Pharmacol. Exp. Ther. **1991,** 257, 706-713.

(11) Rocha, B.A., Fumagalli, F., Gainetdinov, R.R., Jones, S., Ator, R., Giros, B., Miller G.W. and Caron, M. Cocaine self-administration in dopamine transporter knockout mice, *Nature Neuroscience*. **1998**, *1*,132-137.

(12) Walsh, S. L.; Cunningham, K. A. Serotonergic mechanisms involved in the discrimination stimulus, reinforcing and subjective effects of cocaine. Psychopharmacol. **1997**, *130*, 41-58.

(13) Carrol, F. I.; Lewin, A. H.; Mascarella, S. W. Dopamine transporter uptake blockers: Structure activity relationships. In neurotransmitter transporters: Structure and function; Reith, M. E. A., Eds.; Human Press: Totowa, NJ, second edition, 381-432, **2002**.

(14) Singh, S. Chemistry, design, and structure-activity relationship of cocaine antagonists. Chem. Rev. **2000**, *100*, 925-1024.

(15) Dutta, A, K.; Zhang, S.; Kolhatkar, R.; Reith, M. E. A. Dopamine transporter as target for drug development of cocaine dependence medications. Eu. J. Pharmacol. **2003**, 479, 93-106.

(16) Dutta, A. K.; Xu, C.; Reith, M. E. A. Structure-Activity Relationship Studies of Novel 4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(3-phenylpropyl)piperidine Analogues: Synthesis and Biological Evaluation at the Dopamine and Serotonin Transporter Sites. *J. Med. Chem.* **1996**, *39*, 749-756.

(17) Dutta, A. K.; Coffey, L. L.; Reith, M. E. A. Highly selective, novel analogues of 4-[2-(diphenylmethoxy)ethyl]-1-benzylpiperidine for the dopamine transporter: Effect of different aromatic substitutions on their affinity and selectivity. *J. Med. Chem.* **1997**, *40*, 35-43.

(18) Dutta, A. K.; Fei, X-S.; Beardsley, P.; Newman, J.; Reith, M. E. A. Structure-Activity Relationship Studies of 4-[2-(Diphenylmethoxy)-ethyl]-1-benzylpiperidine Derivatives and their N-analogues: Evaluation of Behavioral Activity of O-and N-Analogues and their Binding to Monoamine transporters. *J. Med. Chem.* **2001**, *44*, 937-948.

(19) Dutta, A. K.; Davis, M.; Fei X-S.; Beardsley, P. M.; Cook, C. D.; Reith M. E. A. Expansion of Structure-Activity Studies in piperidine analogues of 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (GBR 12935) compounds by altering substitutions in the N-benzyl moiety and behavioral pharmacology of selected molecules.

J. Med. Chem. 2002, *45*, 654-662.

(20) Dutta, A. K.; Davis, M. C.; Reith, M. E. A. Rational Design and synthesis of novel conformationally constrained 2,5-disubstituted cis- and tras-piperidine derivatives exhibiting differential activity for the dopamine transporter. *Bioorg. Med. Lett.* **2001**,*11*, 2337-2340.

(21) Kolhatkar R B, Ghorai S K, George C, Reith M. E. A, Dutta A K. Interaction of *cis*-(6-benzhydryl-piperidin-3-yl)-benzyl-amine analogs with monoamine transporters: Structure Activity Relationship study of structurally constrained 3,6-disubstituted piperidine analogs of (2,2-diphenylethyl)-[1-(4-fluorobenzyl)piperidine-4-ylmethyl]amine. *J. Med. Chem.* 2003, 46, 2205-2215.

(22) Zhang S, Reith M E A, Dutta A K. Design, synthesis, and activity of novel cis- and trans-3,6-disubstituted pyran biomimetics of 3,6-disubstituted piperidine as potential ligands for the dopamine transporter. *Bioorg. Med. Chem. Lett. 2003,* 13, 1591-1595.

(23) Meltzer, P. C., Liang, A. Y., Blundell, P., Gonzalez, M. D., Chen, Z., George, C., Madras, B. K. 2-Carbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes: Potent non-nitrogen inhibitors of monoamine transporters. *J. Med. Chem.* **1997**, 40, 2661-2673.

(24) Simoni, D., Roberti, M., Rondanin, R., Baruchello, R., Rossi, M., Invidiata, F. P., Merighi, S., Varani, K., Siniscalchi. Effects of two-carbon bridge region methoxylation of benztropine: Discovery of novel chiral ligands for the dopamine transporter. *Bioorg. Med. Chem. Lett.* 2001, 11, 823-827.

(25) S. Danishefsky, T. Kitahara. A Useful Diene for the Diels-Alder Reaction. *J. Am. Chem. Soc.*, 1974, 96, 7807-7808

(26) Varelis, P., Graham, A. J., Johnson, B. L., Skelton, B. W., White. A. H. Stereoselective Synthesis of (±)-(cis-6-Methyltetrahydropyran-2-yl)acetic Acid. *Aust. J. Chem.*, 1997, 47, 1735-1739.

(27) Bernet, B., Piantini, U., Vasella, A. Determination of the *gauche* effect of 3-acetamido- and 3-acetoxy-piperidine and –tetrahydropyran by ^{1}H-n.m.r. spectroscopy. *Carbohydrate Research*, 1990, 204, 11-25.

(28) Gurjar, M. K., Murali Krishna, L., Sridhar Reddy, B., Chorghade, M. S. A Versatile Approach to Anti-Asthmatic Compound CMI-977 and its Six-Membered Analogue. *Synthesis*, 2000, No.4, 557-560.

(29) Gurjar, M. K., Murali Krishna, L., Sridhar Reddy, B., Chorghade, M. S. A Versatile Approach to Anti-Asthmatic Compound CMI-977 and its Six-Membered

Analogue. *Synthesis*, 2000, No.4, 557-560.
(30) Sturino, C. F., Wong, J. C. The Ring-Closing Metathesis of Vinyl Ethers with Grubbs' Catalyst for the Synthesis of Dihydropyrans. *Tetrahedron Letters*, 1998, 39, 9623-9626.
(31) Brown, H. C., Vara Prasad, J. V. N., Zee, S-H. Hydroboration. 71. Hydroboration of Representative Heterocyclic Olefins with Borane-Methyl Sulfide, 9-Borabicyclo[3.3.1]nonane Dicyclohexylborane, and Disiamylborane. Synthesis of Heterocyclic Alcohols. *J. Org. Chem.* 1985, 50, 1582-1589.
(32) Carroll, F. I., Mascarella, S. W., Kuzemko, M. A., Gao, Y., Abraham, P., Lewin, A., Boja, J. W., Kuhar, M. J. Synthesis, ligand binding, and QSAR (CoMFA and classical) study of 3 β-(3'-substituted phenyl)-,3 β-(4'-substituted phenyl)-, and 3 β-(3',4'-disubstituted phenyl)tropane-2β-carboxylic acid methyl esters. J. Med. Chem. 1994, 37, 2865-2873.
(33) Deutsch, H. M. S., Q., Gruszecka-Kowalik, E., Schweri, M. M. Synthesis and pharmacology of potential cocaine antagonists. 2. Structure-Activity relationship studies of aromatic ring-substituted methylphenidate analogs. J. Med. Chem. 1996, 39, 1201-1209.
(34) N. Chen and M.E.A. Reith: Structure-function relationships for biogenic amine neurotransmitter transporters. In: Neurotransmitter Transporters: Structure, Function, and Regulation, 2nd edition (M.E.A. Reith, ed.), Humana Press Inc., Totowa, NJ, pp. 53-109 (2002).□(35) Torres G. E, Gainetdinov R. R, Caron M. G. Plasma membrane monoamine transporters: structure, regulation and function. Nat Rev Neurosci. 2003 Jan;4(1):13-25.

FIGURES/TABLES/REACTION SCHEMES for PART I:

Figure 1: Molecular structure of dopamine transporter blockers.

Figure 2: Rational modification of flexible piperidine molecules into constrained structures.

Figure 3: Three-dimensional orientation of the lowest energy conformers and the overlapped ligands: A: lowest energy conformer from compound **7a**; B: lowest conformer from compound **16b**; C overlapped ligands based on two conformers A and B.

Table 1. Affinity of Drugs at Dopamine, Serotonin, and Norepinephrine Transporters in Rat Striatum.

compd	DAT binding, IC_{50}, nM, [^{3}H]Win 35, 428 [a]	SERT binding, IC_{50}, nM, [^{3}H]citalopram[a]	NET binding, IC_{50}, nM [^{3}H]nisoxetine[a]	DAT uptake, IC_{50}, nM, [^{3}H]DA[a]
cocaine	266±37	737±160	3,130±550	
GBR 12909	10.6±1.9	132±0	496±22	
I	32.5±12.6	2,220±590	1,020±72	45.7±5.1
7a	1,302±68	3,313±170	5,101±1,037	
7b	1,581±283	4,778±1,808	17,543±2,153	
16a	313±71[b]	8,410±163	12,700±3,180	
16b	163±29[b]	1,860±22	232±46	156±36
16c	52.6±5.9[b]	863±52	1,580±89	58.6±13.2
16d	38.3±3.9[b]	738±164	968±98	102±7

16e	84±6.5	1,180±269	1,550±682	59.5±11.6
16f	794±111	2,590±1,410	1,860±847	
16g	227±67	1,640±448	401±96	135.2±47.5
16h	78.4±9	398±22	22.6±1.4	
16i	400±31	780±84	144±25	880 ± 136
16j	368±85	3,520±831	695±142	
16k	303 ± 14	1577 ± 97	274 ± 29	242 ± 39
16l	202 ± 13	2363 ± 92	592 ± 12	251 ± 14
16m	319 ± 21	2477 ± 145	234 ± 17	500 ± 34
16n	587 ± 66	325 ± 20	56 ± 6	
160	151 ± 13	1690 ± 169	123 ± 10	155±14
16p	129 ± 58	3,950±660	5,210±678	
15	777±41			251±31

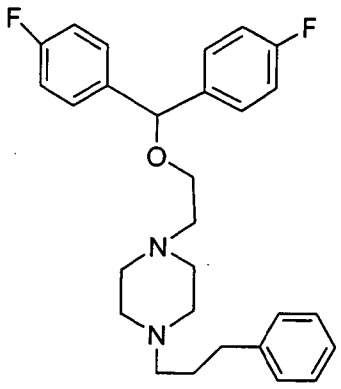
a. For binding, the DAT was labeled with [^{3}H]WIN 35, 428, the SERT with [^{3}H]citalopram and the NET with [3H]nisoxetine. For uptake by DAT, [3H]DA accumulation was measured. Results are average ± SEM of three to eight independent experiments assayed in triplicate. b. See reference # 22

Table 2. Selectivity of Various Drugs for Their Activity at Monoamine Transporters

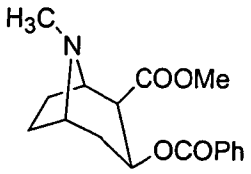
compound	SERT binding/ DAT binding	NET binding/ DAT binding	[3H]DA uptake/ DAT binding
Cocaine	2.8	11.8	
GBR 12909	12.5	46.8	
I	68.3	31.4	1.4
7a	2.5	3.9	
7b	3	11.1	
16a	26.9	40.6	
16b	11.4	1.4	0.96
16c	16.4	30	1.1
16d	19.3	25.3	2.7
16e	14	18.5	0.71

16f	3.3	2.3	
16g	7.2	1.8	0.60
16h	5.1	0.29	
16i	1.9	0.36	
16j	9.6	1.9	
16k	5.20	0.90	0.79
16l	11.69	2.93	1.24
16m	7.76	0.73	1.56
16n	0.55	0.09	
16o	11.19	0.81	1.02
16p	30.6	40.4	
15			0.32

Figure 1



GBR 12909



(-)-Cocaine

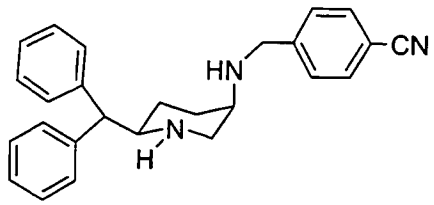


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Figure 2

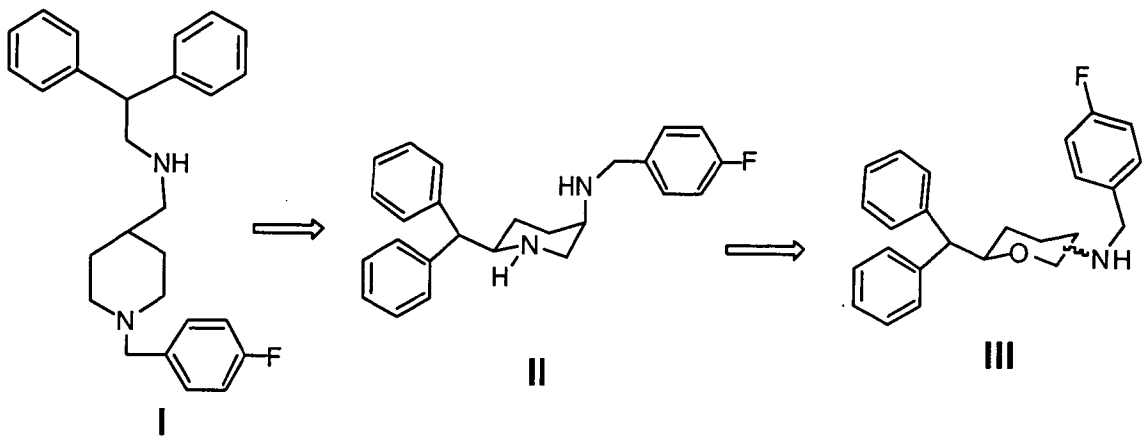
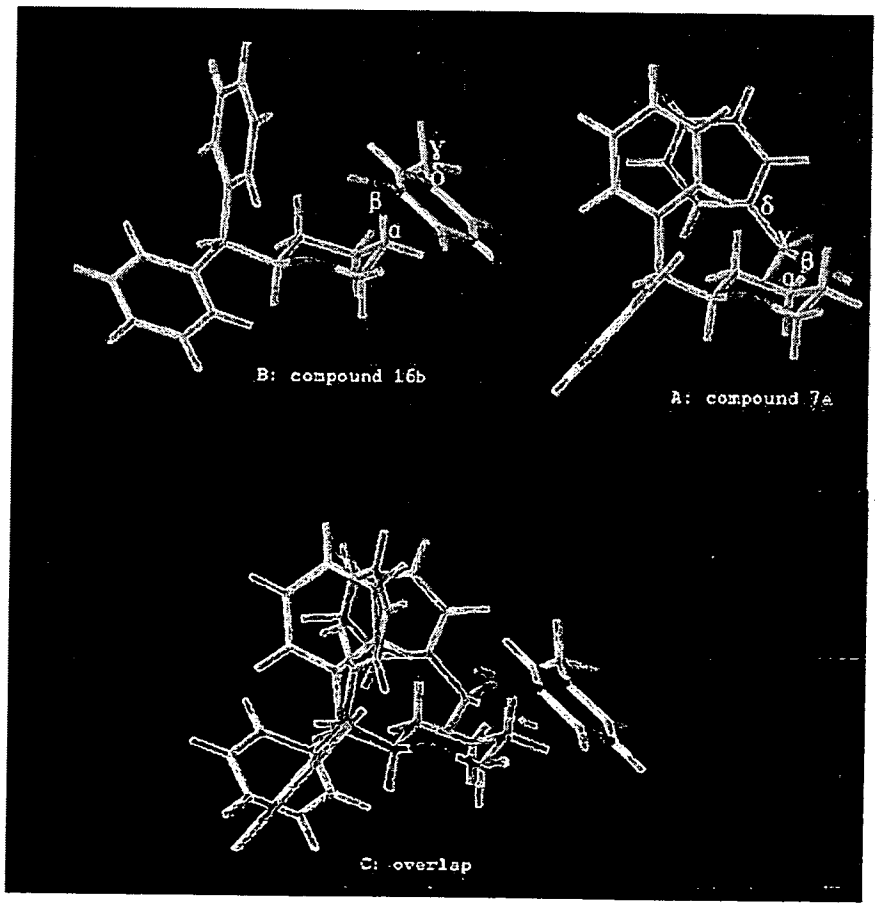
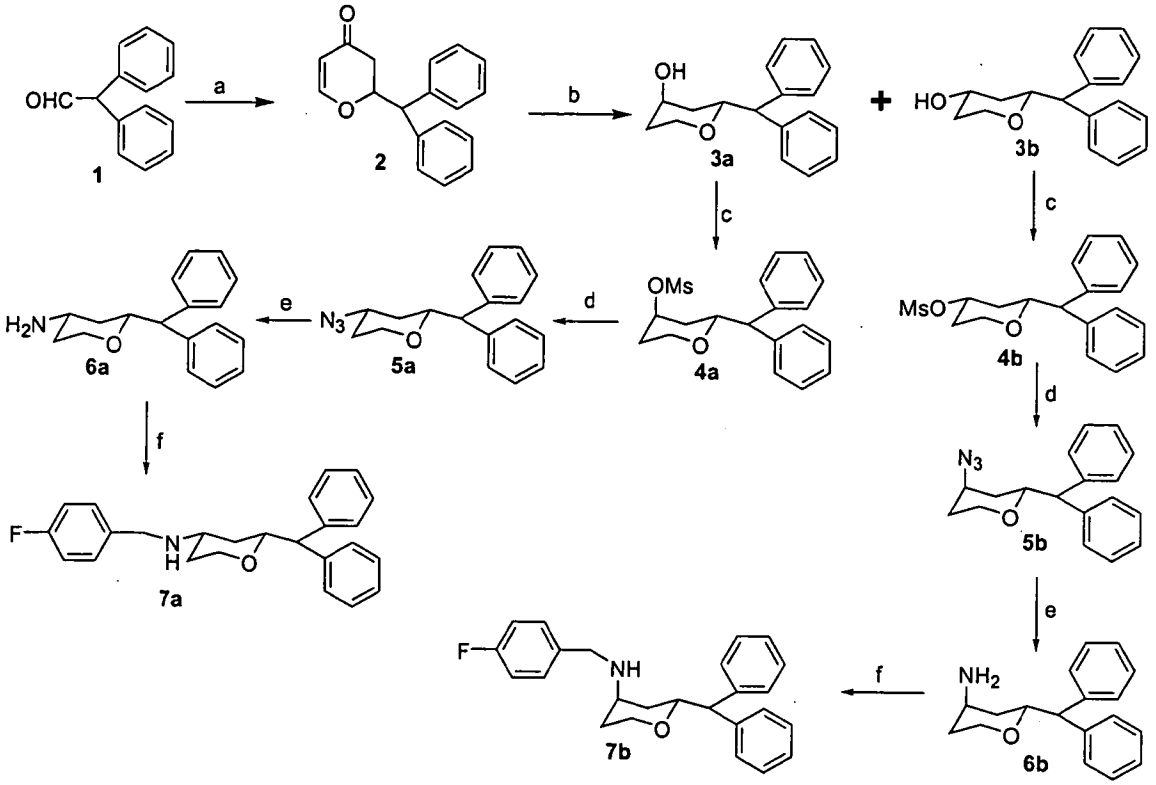


Figure 3

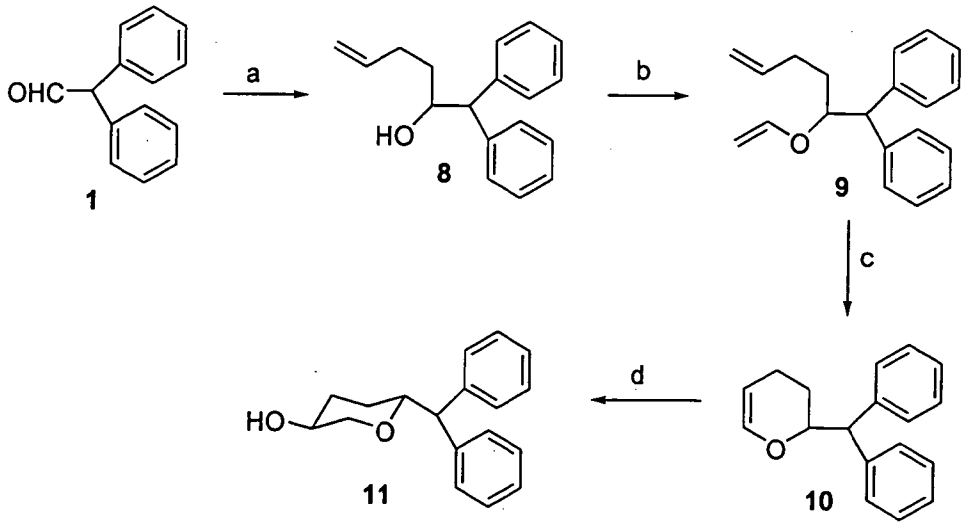


Scheme 1



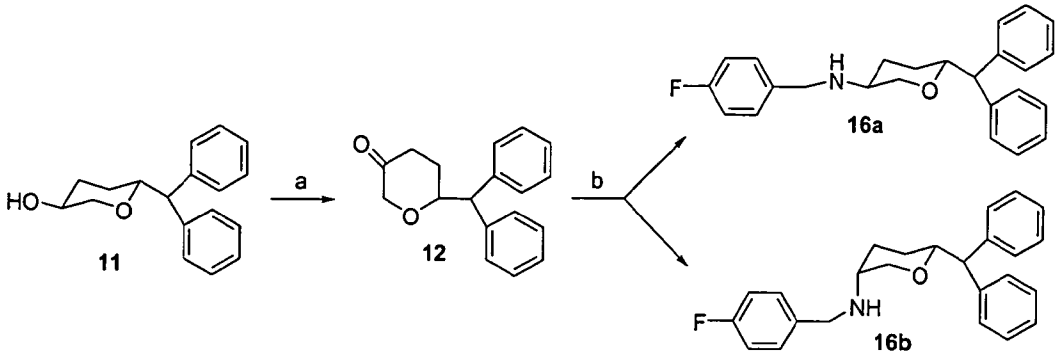
(a) Danishefsky's diene, BF_3/Et_2O (b) BF_3/Et_2O, $NaCNBH_3$/THF (c) CH_3SO_2Cl, Et_3N/CH_2Cl_2
(d) NaN_3/DMF (e) H_2/Pd-C/MeOH (f) 4-Fluorobenzaldehyde, AcOH, $NaCNBH_3/ClCH_2CH_2Cl$

Scheme 2



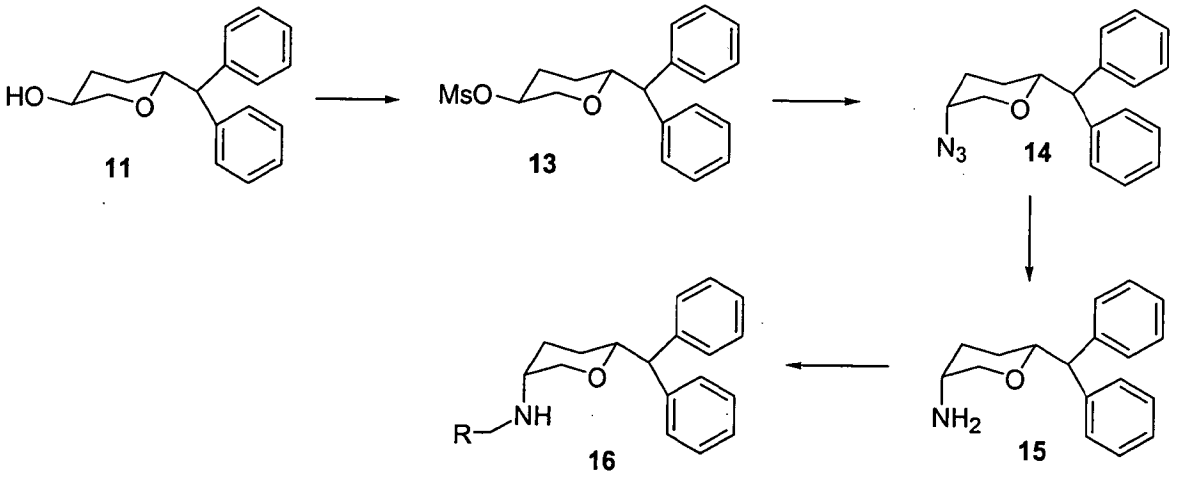
(a) 4-bromo-1-butene, Mg, Et_2O (b) Ethyl vinyl ether, $Hg(OCOCF_3)_2$
(c) Grubb's catalyst, Benzene (d) 9-BBN/THF, NaOH, H_2O_2

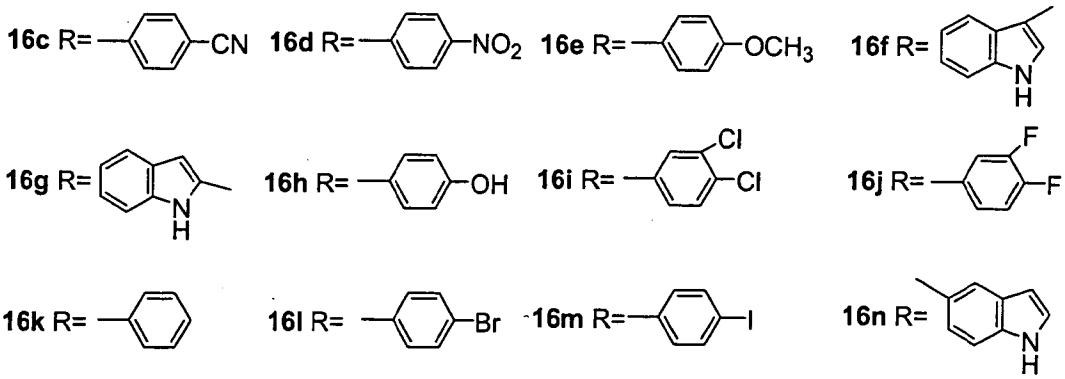
Scheme 3



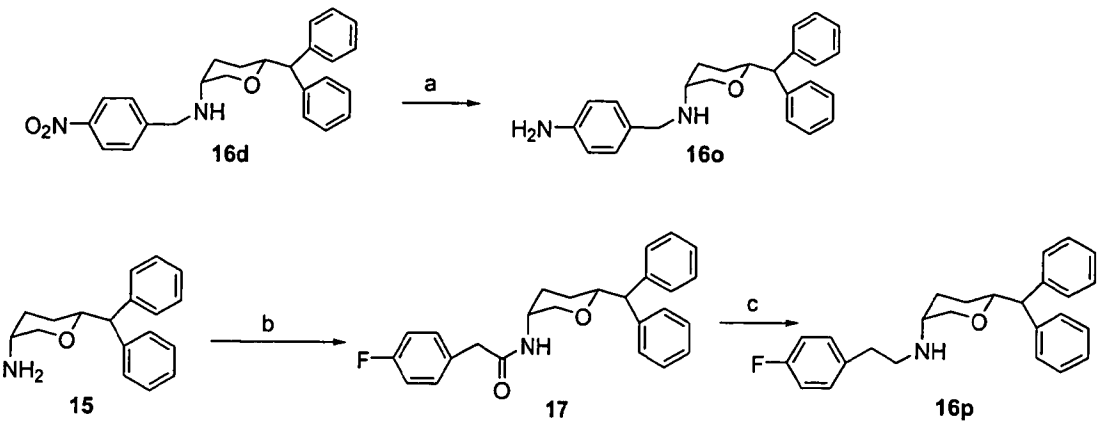
(a) oxalyl chloride, DMSO, Et_3N/CH_2Cl_2 (b) 4-fluorobenzylamine, AcOH, $NaCNBH_3/ClCH_2CH_2Cl$

Scheme 4





Scheme 5



(a) $SnCl_2$¡2H_2O/EtOH/EtOAc (b) 4-fluorophenylacetyl chloride, Et_3N/CH_2Cl_2 (d) $NaBH_4$, BF_3¡Et_2O/THF

Elemental Analysis Results of Final Compounds:

Compound	Found			Calculated		
	C	H	N	C	H	N
7a	69.57	6.07	3.01	69.66	6.06	3.01
7b	69.68	6.17	3.04	69.66	6.06	3.01
16a 0.65H_2O	67.93	6.02	3.02	67.96	6.19	2.94
16b	69.60	6.09	2.97	69.66	6.06	3.01
16c	70.92	6.00	5.88	71.17	5.97	5.93
16d	65.61	5.79	5.64	65.84	5.73	5.69
16e	70.45	6.57	2.97	70.42	6.54	2.93
16f 0.5H_2O	70.68	6.32	5.55	70.29	6.31	5.65
16g 0.5H_2O	70.68	6.32	5.55	70.29	6.31	5.65
16h	70.36	6.68	3.03	69.96	6.31	3.02
16i	62.52	5.23	2.66	62.80	5.27	2.71
16j	67.09	5.70	2.88	67.07	5.63	2.90
16k	71.86	6.65	3.11	71.88	6.57	3.10
16l	61.57	5.36	2.65	61.60	5.36	2.66
16m	56.43	4.94	2.45	56.55	4.92	2.45
16n	70.05	6.29	5.40	70.29	6.30	5.65
16o 0.3H_2O	62.11	5.73	4.92	62.42	5.89	5.02
16p	69.76	6.34	2.90	70.13	6.31	2.92
15 0.2H_2O	70.41	7.57	4.17	70.32	7.34	4.55

PART II

FURTHER SYNTHESIS AND CHARACTERIZATION OF PYRAN DERIVATIVES FOR MONOAMINE TRANSPORTER SYSTEMS AS ANTIDEPRESSANT AGENTS

Chemistry

Scheme 1 describes the synthesis of the two enantiomers of 2-benzhydryl-oxirane. Starting from diphenylacetaldehyde **1**, wittig reaction gave olefin **2** in moderate yield . Epoxidation of **2** with mCPBA delivered the racemic 2-benzhydryl-oxirane **3** in good yield. The racemate 2-benzhydryl-oxirane **3** was resolved by HKR reaction with (R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt catalyst efficiently to give (2R)-2-benzhydryl-oxirane **3a** and (2S)-3,3-diphenyl-propane-1,2-diol **4** in high enantio-excess ratio. Mitsunobu reaction of diol (2S)-3,3-diphenyl-propane-1,2-diol **4** with DEAD and TPP in benzene furnished (2S)-2-benzhydryl-oxirane **3b** in good yield

The synthesis of compounds **(-)9a, (-)9b, (-)9c,** and **(-)9d** was described in **scheme 2.** Opening of (2R)-2-benzhydryl-oxirane **3a** with copper reagent produced in situ from vinylmagnesium bromide and copper (I) iodide gave (2S)-1,1-diphenyl-pent-4-en-2-ol **5a** in good yield. O-alkylation with allyl bromide under basic condition delivered (2S)-1,1-diphenyl-2-allyloxy-pent-4-ene **6a** in good yield. Ring cyclic metathesis (RCM) reaction in presence of Grubb's catalyst produced cyclic (2S)-2-benzhydryl-3,6-dihydro-2H-pyran **7a** in high yield. Epoxidation of (2S)-2-benzhydryl-3,6-dihydro-2H-pyran **7a** with mCPBA gave two diastereomers: trans-epoxide (1S,4S,6R)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8a** and cis-epoxide (1R,4S,6S)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8b** which were separated by column chromatography. Opening of trans-(1S,4S,6R)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8a** with different amines in ethanol under refluxing condition furnished the final products **(-)9a, (-)9c,** and **(-)9d** in optically pure form. On the other hand, in a different regioselective opening of cis-(1R,4S,6S)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8b** with p-methoxy benzylamine produced optically pure product (3R,4R,6S)-6-benzhydryl-4-(4-methoxy-benzylamino)-tetrahydro-pyran-3-ol **(-)9b** in good yield.

In our synthetic strategy, we wanted to exploit regioselective opening mechanism of cis and trans epoxide rings in 2-substituted pyran derivatives by nucleophilic amines. It

was expected from work by previous authors that a trans diaxial epoxide ring opening will take place if the the pyran ring exist in a semi-rigid configuration. 1H NMR data indicates that the diphenyl group in our pyran derivatives oriented in an equatorial position. Therefore, we expected that in our compounds trans-diaxial ring opening will take place. Regioselectivity in pyran epoxide ring opening was observed earlier as cis and trans epoxide produced rigioselectively two different trans products. In our case, we wanted to observe the influence of benzhydril substituent at the 2-position of pyran ring in regio- and stereo-selective opening of the epoxide ring. It is evident that epoxide ring opening took place with complete regioselectivity depending upon the stereochemistry of the epoxide molecule. Thus, cis-epoxide 8a, underwent trans diaxial opening with nucleophilic amine at the position 3 in the same phase as the biphenyl moiety in the pyran ring giving rise to compounds 9(a), 9(c), and 9(d).

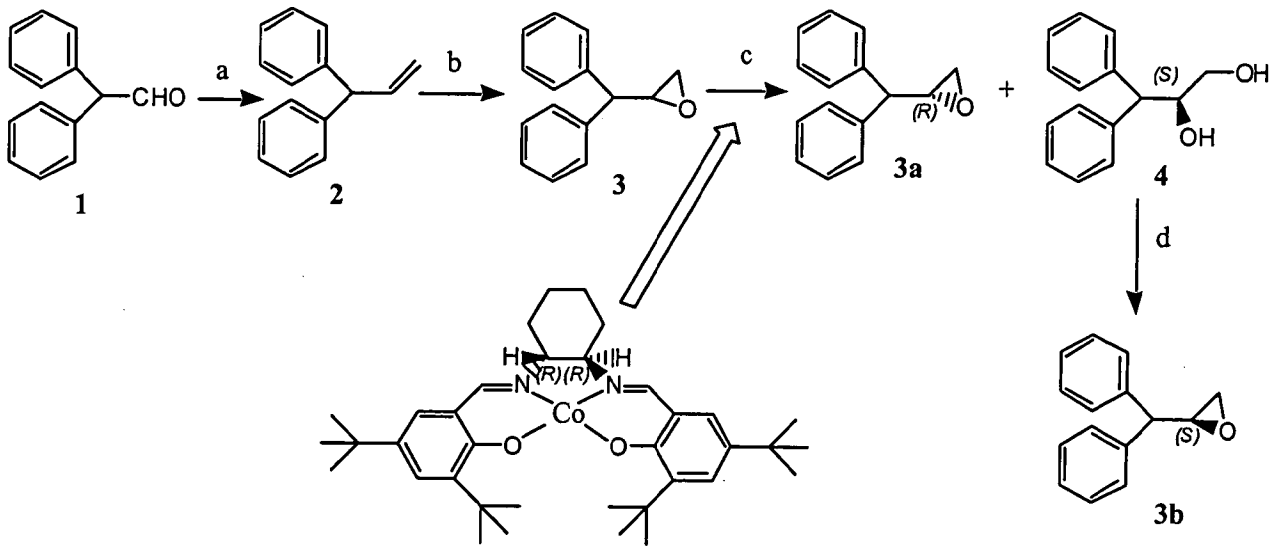
Scheme 3 describes the synthesis of compounds **(+)9a**, **(+)9b**, **(+)9c**, **(+)9d**, **(+)9e**, and **(+)9f** starting from cis-(1R,4R,6S)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8c** and trans-(1S,4R,6R)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8d** in the same way as described in the **scheme 2.**

The synthesis of (2S, 4R, 5R)-2-benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol (-)12 and (2R, 4S, 5S)-2-benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol **(+)12** is shown in **Scheme 4**. The cis epoxide derivative (1S,4S,6R)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8a** was reacted with NaN_3 in the presence of NH_4Cl in THF-H_2O to give regioselectively only (2S, 4R, 5R)-2-benzhydryl-5-azido-tetrahydro-pyran-4-ol **10a**. Compound **10a** was hydrogenated in presence of a palladium-C catalyst in methanol to produce amine **11a** in good yield. Reductive amination of **11a** with 4-hydroxy-benzaldehyde produced (2S, 4R, 5R)-2-benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol **(-)12**. Same procedure starting with trans-(1R,4R,6S)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8c** produced regioselectively the enantiomeric compound (2R, 4S, 5S)-2-benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol **(+)12** in good yield.

Synthesis of cis-(3S, 6S)-(6-benzhydryl-tetrahydro-pyran-3-yl)-(4-hydroxy-benzyl)-amine **(-)17** and cis-(3R, 6R)-(6-benzhydryl-tetrahydro-pyran-3-yl)-(4-hydroxy-benzyl)-amine **(+)17** is described in **Scheme 5** and **6**. Cis-(1S,4S,6R)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8a** was reduced by $LiAlH_4$ in dry pentane to give trans-(3R, 6S)-6-

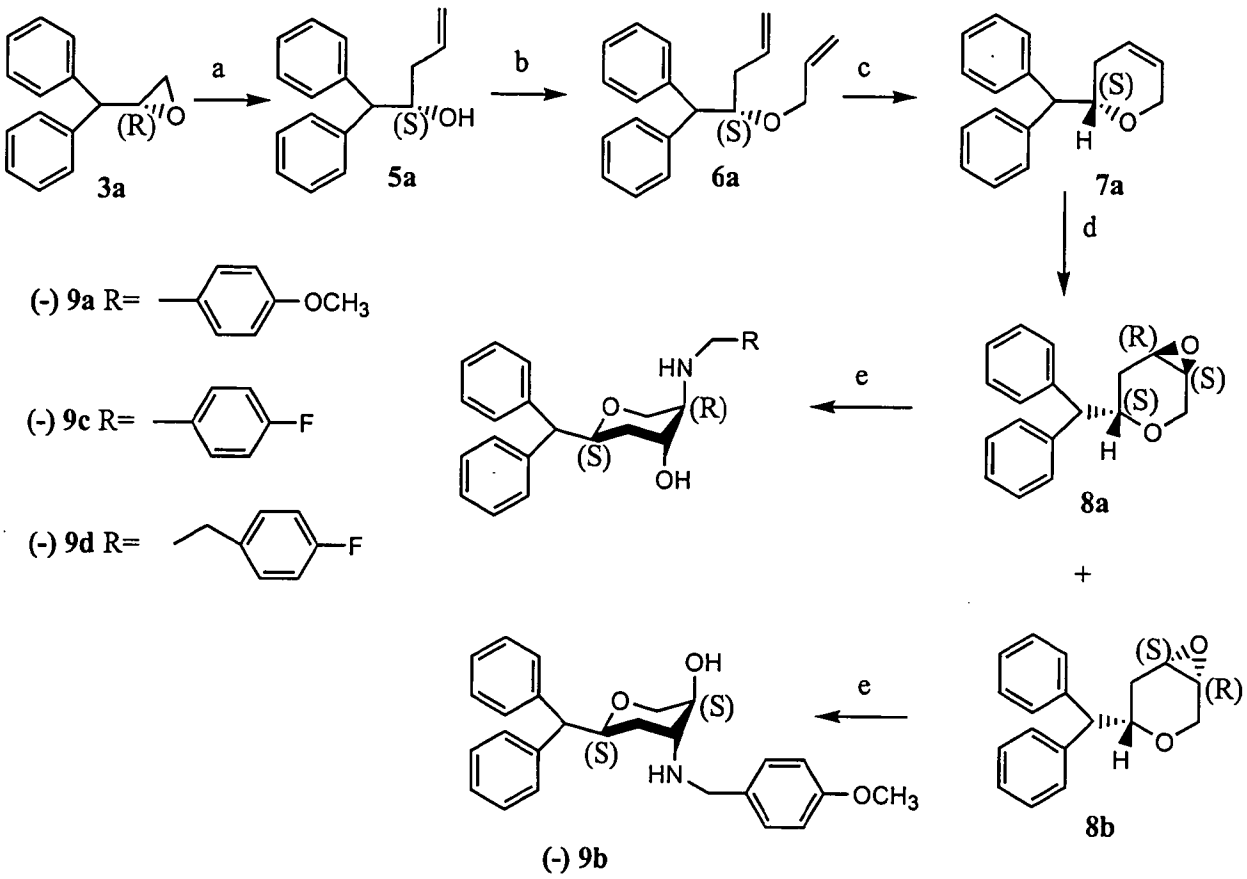
benzhydryl-tetrahydro-pyran-3-ol **13a**. Trans alcohol compound **13a** was then converted into cis-(3S, 6S)-3-amino-6-benzhydryl-tetrahydro-pyran **16a** by a three-step reactions. Thus mesylation of alcohol produced intermediate mesylate derivative **14a** which on azido displacement reaction produced azido derivative with inverted stereochemistry **15a**. Hydrogenation of azido to amine produced compound **16a**. Reductive amination of compound **16a** with 4-hydroxy-benzylaldehyde gave cis-(3S, 6S)-(6-benzhydryl-tetrahydro-pyran-3-yl)-(4-hydroxy-benzyl)-amine **(-)17**. Same procedure starting from (1R,4R,6S)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8c** produced cis-(3R, 6R)-(6-benzhydryl-tetrahydro-pyran-3-yl)-(4-hydroxy-benzyl)-amine **(+)17**. In the synthesis of compound **(+)-17**, the intermediate **13b** could also be synthesized via an alternative procedure starting from (1S,4R,6R)-4-benzhydryl-3,7-dioxa-bicyclo[4,10]heptane **8d**. Compound **8d** was reduced by $LiAlH_4$ in the presence of 12-crown-4 in dry pentane to give cis-(3R, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol **18**. Compound **18** was converted to compound **13b** through two steps reaction: Mesylation, KO_2 substitution and work-up.

Scheme 1



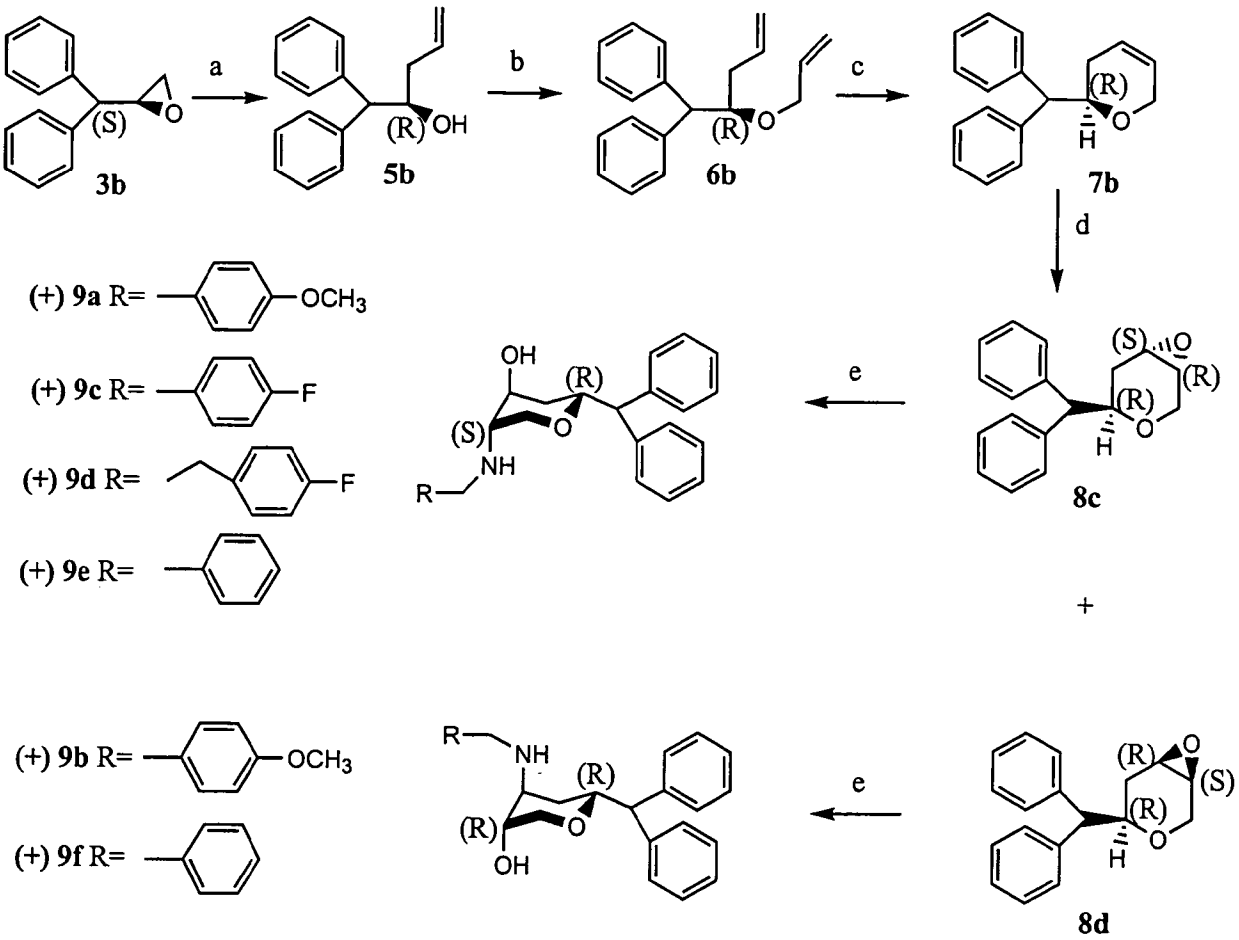
a) methyldiphenylphosphonium bromide/BuLi/THF b) mCPBA/CH_2Cl_2
c) Jacobsen's catalyst/H_2O d) TPP/DEAD/benzene

Scheme 2



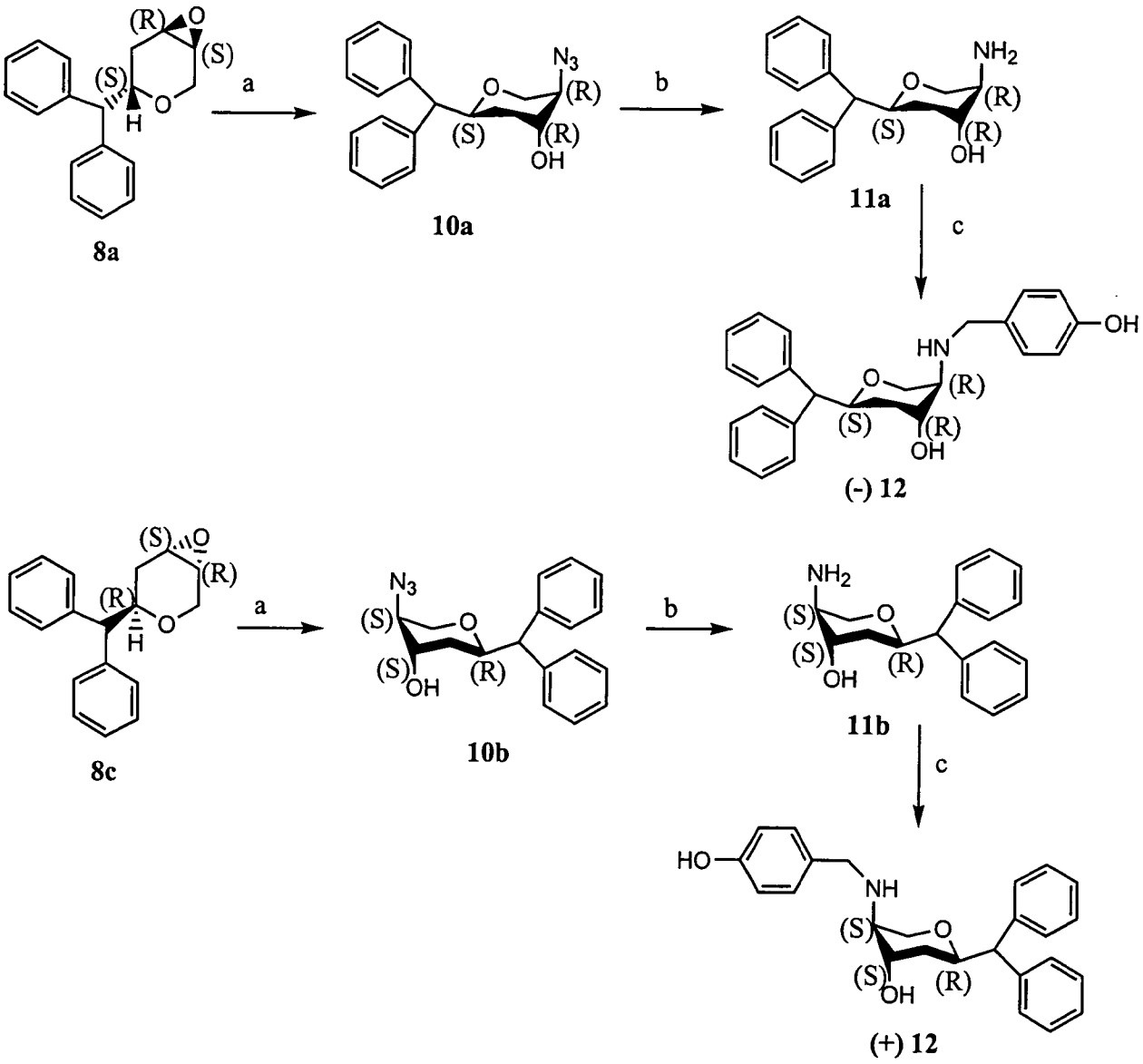
a) vinyl magnesium bromide/CuI/THF b) NaH/allyl bromide/DMF c) Grubbs' catalyst/benzene d) mCPBA/CH_2Cl_2 e) amine/ethanol

Scheme 3



a) vinyl magnesium bromide/CuI/THF b) NaH/allyl bromide/DMF c) Grubbs' catalyst/benzene d) mCPBA/CH_2Cl_2 e) amine/ethanol

Scheme 4

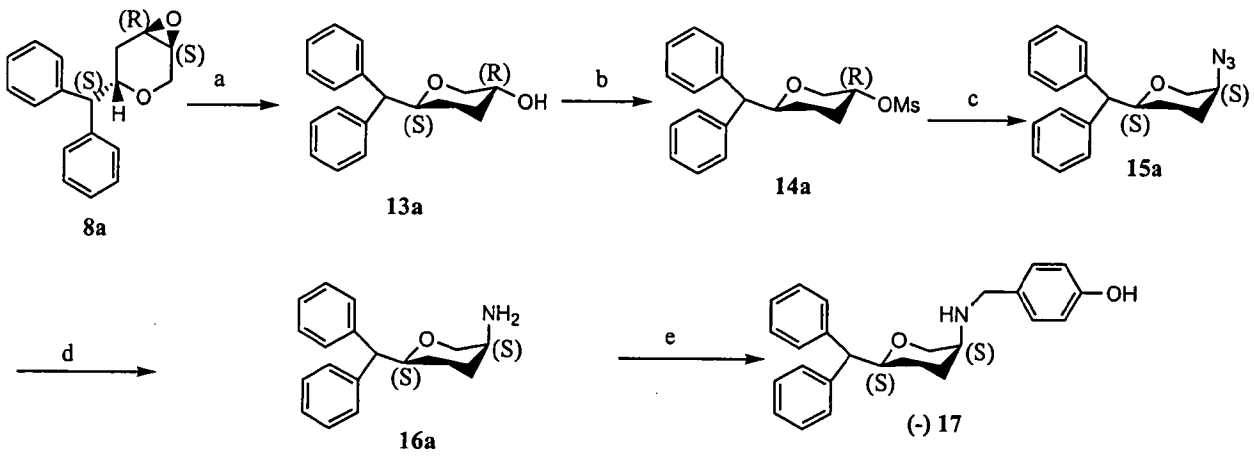


8a 10a 11a (-) 12

8c 10b 11b (+) 12

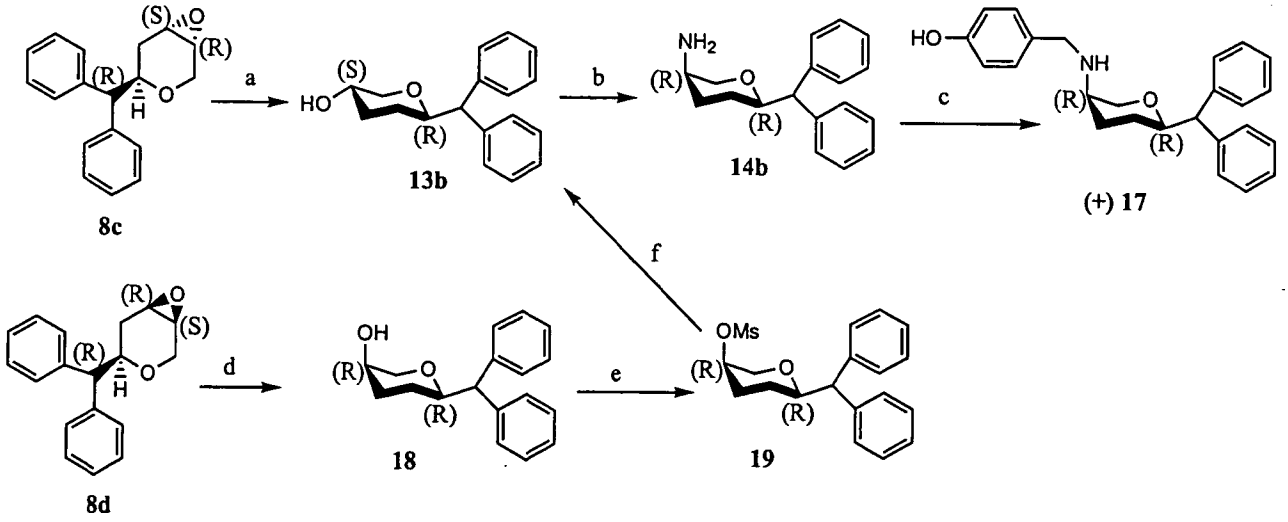
a) $NaN_3/NH_4Cl/THF\text{-}H_2O$ b) $H_2/Pd\text{-}C$ c) 4-hydroxy-benzylaldehyde/AcOH/$NaCNBH_3$

Scheme 5



a) $LiAlH_4$/pentane; b) $MeSO_2Cl/Et_3N/CH_2Cl_2$; c) NaN_3/DMF; d) H_2/Pd-C
e) 4-hydroxybenzylaldehyde/AcOH/$NaCNBH_3$

Scheme 6



a) $LiAlH_4$/pentane; b) i. $MeSO_2Cl/Et_3N/CH_2Cl_2$, ii. NaN_3/DMF, iii. H_2/Pd-C
c) 4-hydroxybenzylaldehyde/AcOH/$NaCNBH_3$; d) $LiAlH_4$/12-crown-4/pentane
e) $MeSO_2Cl/Et_3N/CH_2Cl_2$ f) KO_2/18-crown-6/DMSO-DMF (iii) HCl/H_2O

Experiment Detail

Synthesis of 3,3-Diphenylpropene (2)

Methyltriphenylphosphonium bromide (4 g, 11.12 mmol) was added over a 15-min period to a mixture of butyllithium (7.3 ml of 1.6 M solution in THF, 11.76 mmol) and dry THF (50

ml) with stirring and under nitrogen atmosphere at ^{0}C.The reaction mixture was stirred for 2h at room temperature and the mixture was then recooled to ^{0}C.Asolution of diphenylacetaldehyde (2.2 g, 11.12 mmol) in dry THF(10 ml) was added to the above mixture for over a 15-min period. The reaction mixture was stirred for 24 h at room temperature which was followed by addition of ethyl ether (200 ml) and the reaction mixture was filtered. The ether extracts were washed with water (3 x50ml), brine (100 ml) and dried over anhydrous sodium sulfate. The crude material was purified by flash chromatography on silical gel (Hexane:Ethyl ether=9:1) to give pure 3,3-diphenylpropene 460 mg (46%).

^{1}HNMR ($CDCl_3$, 400MHz) 4.82(d, J=6.4Hz, 1H, H-3) 5.08(d, J=17.2Hz, 1H, H-1) 5.31(d, J=12Hz, 1H, H-1) 6.39(m, 1H, H-2) 7.2-7.4(m, 10H, aromatic-H)

^{13}CNMR ($CDCl_3$, 100MHz) 55.30, 116.69, 126.67, 128.73, 128.92, 140.94, 143.59

Synthesis of 2-Benzhydryl-oxirane (3)

A flask was charged with 3,3-diphenylpropene (5.1 g, 26.3 mmol) in 100 ml CH_2Cl_2. It was followed by by portionwise addition ofmCPBA (9.1 g, 70% purity, 52.6 mmol) at ^{0} C. The mixture was stirred at room temperature for 24h and the reaction was then quenched with 30 ml 1M Na_2SO_3. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 ml). The combined organic phase was washed in turn with saturated NaHCO3, brine, and then dried over anhydrous Na_2SO_4. Purification by flash chromatography (Hexane/ether=9:1) gave pure 2-benzhydryl-oxirane 4.7g (85%).

^{1}HNMR ($CDCl_3$, 400MHz) 2.54(m, 1H, H-1) 2.87(m, 1H, H-1) 3.54(m, 1H, H-2) 3.86(d, J=7.6Hz, 1H, Ph_2CH), 7.2-7.4(m, 10H, aromatic-H)

^{13}CNMR ($CDCl_3$, 100MHz) 46.80, 53.58, 55.17, 127.06, 127.14, 128.70, 128.81, 141.28

Resolution of racemic 2-benzhydryl-oxirane by HKR reaction

A mixture of (R,R)-(-)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexane diaminocobalt (II) (0.22 g, 0.37 mmol, 0.8%), toluene (5 ml), and acetic acid (0.044 g, 0.74 mmol) was stirred for 1h at room temperature. The solvent was removed in vacuo and the

residue was dried. 2-Benzhydryl-oxirane (9.6 g, 45.7 mmol) was added in one portion and stirred, the mixture was then cooled under ice-bath. H_2O (0.58 g, 32 mmol) was slowly added over a 30-min period. After addition of water the ice bath was removed and the reaction mixture was stirred at room temperature for 72h. Compouds were separated via flash chromatography on slica gel column to give (2R)-2-benzhydryl-oxirane **(3a)** 4.5 g ($[\alpha]_D$=(+)9.58, c=1, MeOH) and (2S)-3,3-diphenyl-propane-1,2-diol **4** 3.53 g ($[\alpha]_D$=(+)48, c=1, MeOH, ee=97%).

The proton and carbon NMR date of (2R)-2-benzhydryl-oxirane was identical to the racemate 2-benzhydryl-oxirane.

^{1}HNMR ($CDCl_3$, 400MHz) 2.54(m, 1H, H-1) 2.87(m, 1H, H-1) 3.54(m, 1H, H-2) 3.86(d, J=7.6Hz, 1H, Ph_2CH), 7.2-7.4(m, 10H, aromatic-H)

^{13}CNMR ($CDCl_3$, 100MHz) 46.80, 53.58, 55.17, 127.06, 127.14, 128.70, 128.81, 141.28

For (2S)-3,3-diphenyl-propane-1,2-diol:

^{1}HNMR ($CDCl_3$, 400MHz) 2.39(bs, 2H, OH) 3.44(m, 1H, H-1) 3.60(m, 1H, H-1), 4.02(D, J=10Hz, 1H, Ph_2CH), 4.44(m, 1H, H-2), 7.16-7.22(m, 10H, aromatic-H).

^{13}CNMR ($CDCl_3$, 100MHz) 55.08, 64.94, 74.26, 127.08, 127.23, 128.35, 128.84, 129.03, 129.17, 141.23, 141.62

Synthesis of (2S)-2-benzhydryl-oxirane (3b)

A solution of (2S)-3,3-diphenyl-propane-1,2-diol (3.5 g, 15.35 mmol), Ph_3P (8.05 g, 30.7 mmol), and DEAD (5.4 g, 30.7 mmol) in benzene (50 ml) was refluxed for 24h. Solvent was removed and the residue was diluted with ethyl ether (200 ml) to precipitate Ph_2PO. The filtrate was concentrated and the residue was chromatographed on silical gel (hex/ether=9:1) to give (2S)-2-benzhydryl-oxirane **3b** 2.5g (78%, ($[\alpha]_D$=(-)9.6, c=1, MeOH). The ^{1}HNMR and ^{13}CNMR were identical with (R)-isomer.

^{1}HNMR ($CDCl_3$, 400MHz) 2.54(m, 1H, H-1) 2.87(m, 1H, H-1) 3.54(m, 1H, H-2) 3.86(d, J=7.6Hz, 1H, Ph_2CH), 7.2-7.4(m, 10H, aromatic-H)

^{13}CNMR ($CDCl_3$, 100MHz) 46.80, 53.58, 55.17, 127.06, 127.14, 128.70, 128.81, 141.28

Procedure A. Synthesis of (2S)-1,1-Diphenyl-pent-4-ene-2-ol (5a)

(2R)-2-benzhydryl-oxirane (0.5 g, 2.38 mmol) **3a** was dissolved in dry THF (5 ml) and was added into a dry THF solution at –78 oC containing CuI (0.045 g, 0.24 mmol) and vinylmagnesium bromide (5.95 ml of 1.0M solution in THF, 5.95 mmol). The reaction mixture was stirred and allowed to reach room temperature over a period of 2h, and then quenched with saturated NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 30 ml). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash chromatography on silica gel (Hexane/Ethyl Ether=4:1) to give 0.4 g (2S)-1,1-diphenyl-pent-4-ene-2-ol(70%, $[\alpha]_D$=(-)25, c=1, MeOH)

^{1}HNMR ($CDCl_3$, 400MHz) 2.14(m, 1H, H-3), 2.33(m, 1H, H-3), 3.93(d, J=8.8Hz, 1H, H-1) 4.44(m, 1H, H-2) 5.1(m, 2H, H-5), 5.9(m, 1H, H-4), 7.16-7.24(m, 10H, aromatic-H)

^{13}CNMR ($CDCl_3$, 100MHz) 39.75, 58.21, 73.06, 118.23, 126.86, 127.08, 128.51, 128.64, 128.92, 129.00, 135.01

Synthesis of (2R)-1,1-diphenyl-pent-4-ene-2-ol (5b)

(2S)-2-benzhydryl-oxirane (0.61 g, 2.91 mmol) was reacted with vinylmagnesium bromide (7.26 ml of 1.0M solution in THF, 7.26 mmol) in the presence of CuI (0.055 g, 0.29 mmol) (Procedure A) to yield (2R)-1,1-diphenyl-pent-4-ene-2-ol 0.48 g (70%, $[\alpha]_D$=(+)26, c=1, MeOH). The ^{1}HNMR and ^{13}CNMR were identical with (2S)-1,1-diphenyl-pent-4-ene-2-ol.

^{1}HNMR ($CDCl_3$, 400MHz) 2.14(m, 1H, H-3), 2.33(m, 1H, H-3), 3.93(d, J=8.8Hz, 1H, H-1) 4.44(m, 1H, H-2) 5.1(m, 2H, H-5), 5.9(m, 1H, H-4), 7.16-7.24(m, 10H, aromatic-H)

^{13}CNMR ($CDCl_3$, 100MHz) 39.75, 58.21, 73.06, 118.23, 126.86, 127.08, 128.51, 128.64, 128.92, 129.00, 135.01

Procedure B. Synthesis of (2S)-1,1-Diphenyl-2-Allyloxy-Pent-4-en (6a)

(2S)-1,1-diphenyl-pent-4-en-2-ol **5a** (0.37 g, 1.57 mmol) was dissolved in dry DMF (2 ml) and was added to a suspension of NaH (60% in miniral oil, 0.13 g, 3.14 mmol) in dry DMF

(20 ml) at 0℃. The reaction mixture was allowed to reach room temperature for over an period of 1h. The reaction mixture was cooled back to 0℃ in ice-bath and neat allyl bromide (0.57 g, 4.71 mmol) was added via syringe. The reaction mixture was removed from ice-bath and stirred overnight at room temperature. The reaction was cooled again to 0 oC and quenched by slowly adding H_2O (20 ml). The resulting mixture was extracted with Et_2O (3 × 50 ml), and the combined organic phase was washed in turn with H_2O, brine, and dried over anhydrous Na_2SO_4. Filtration followed by concentration gave crude product as light orange oil. Purification by chromatography (hexane/ethyl ether=10:1) gave 0.37g (2S)-1,1-Diphenyl-2-Allyloxy-Pent-4-en (85%, $[\alpha]_D$=(+)19.7, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 500MHz) 2.26(m, 1H, H-3), 2.38(m, 1H, H-3), 3.74(m, 1H, H-3'), 3.96(m, 1H, H-3'), 4.1(m, 2H, H-1, H-2), 5.0-5.16(m, 4H, H-5, H-1'), 5.71(m, 1H, H-2'), 5.93(m,1H, H-4), 7.2-7.46(m, 10H, aromatic-H).

^{13}CNMR ($CDCl_3$, 125MHz) 37.27 56.24 71.74 81.80 116.71 117.63 126.49 126.62 128.38 128.70 128.83 129.36 135.21 142.26 142.87

Synthesis of (2R)-1,1-Diphenyl-2-Allyloxy-Pent-4-en (6b)

(2R)-1,1-diphenyl-pent-4-en-2-ol **5b** (0.42 g, 1.75 mmol) was reacted with allyl bromide (0.63 g, 5.25 mmol) (Procedure B) to yield (2R)-1,1-Diphenyl-2-Allyloxy-Pent-4-en **6b,** 0.43 g (87%, $[\alpha]_D$=(-)20, c=1, MeOH). The ^{1}HNMR and ^{13}CNMR were identical with (2R)-1,1-diphenyl-2-alluloxy-pent-4-en shown above.

^{1}HNMR ($CDCl_3$, 500MHz) 2.26(m, 1H, H-3), 2.38(m, 1H, H-3), 3.74(m, 1H, H-3'), 3.96(m, 1H, H-3'), 4.1(m, 2H, H-1, H-2), 5.0-5.16(m, 4H, H-5, H-1'), 5.71(m, 1H, H-2'), 5.93(m,1H, H-4), 7.2-7.46(m, 10H, aromatic-H).

^{13}CNMR ($CDCl_3$, 125MHz) 37.27 56.24 71.74 81.80 116.71 117.63 126.49 126.62 128.38 128.70 128.83 129.36 135.21 142.26 142.87

Procedure C. Synthesis of (2S)-2-benzhydryl-3,6-dihydro-2H-pyran (7a)

Into a solution of of (2S)-1,1-Diphenyl-2-Allyloxy-Pent-4-en **6a** (0.19 g, 0.68 mmol) in dry benzene was added Grubb catalyst (0.028 g, 0.034 mmol, 5%) and the solution was refluxed under N_2 for the 20h. The solvent was removed, and the residue was purified by flash chromatography (hexane/ether=9:1) to give 0.15 g (2S)-2-benzhydryl-3,6-dihydro-2H-pyran, **7a**

(88%, $[\alpha]_D$=(-)79.3, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.82(m, 1H, H-3) 2.09(m, 1H, H-3) 4.0(d, J=8.8Hz, 1H, Ph_2CH) 4.23(m, 2H, H-6) 4.32(dt, J=2.4Hz, 9.6Hz, H-2) 5.77(m, 2H, H-4, H-5) 7.16-7.26(m, 10H, aromatic-H)

^{13}CNMR ($CDCl_3$, 100MHz) 31.10 51.82 55.52 56.66 67.86 68.03 74.20 126.63 126.86 127.38 128.35 128.81 128.57 128.65 128.74 128.96 142.18 142.37

Synthesis of (2R)-2-Benzhydryl-3,6-dihydro-2H-pyran (7b)

(2R)-1,1-Diphenyl-2-Allyloxy-Pent-4-en **6b** (0.25 g, 0.90 mmol) was cyclized in the presence of Grubb's catalyst (0.037 g, 0.045 mmol) (Procedure C) to produce (2R)-2-Benzhydryl-3,6-dihydro-2H-pyran **7b** 0.2 g (89%, $[\alpha]_D$=(+)80.8, c=1, MeOH) The ^{1}HNMR and ^{13}CNMR were identical with (2S)-2-benzhydryl-3,6-dihydro-2H-pyran **7a**.

^{1}HNMR ($CDCl_3$, 400MHz) 1.82(m, 1H, H-3) 2.09(m, 1H, H-3) 4.0(d, J=8.8Hz, 1H, Ph_2CH) 4.23(m, 2H, H-6) 4.32(dt, J=2.4Hz, 9.6Hz, H-2) 5.77(m, 2H, H-4, H-5) 7.16-7.26(m, 10H, aromatic-H)

^{13}CNMR ($CDCl_3$, 100MHz) 31.10 51.82 55.52 56.66 67.86 68.03 74.20 126.63 126.86 127.38 128.35 128.81 128.57 128.65 128.74 128.96 142.18 142.37

Procedure D. Synthesis of (1S, 4S, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane (8a) and (1R, 4S, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane (8b)

Into the solution of (2S)-2-benzhydryl-3,6-dihydro-2H-pyran **7a** (0.15 g, 0.6 mmol) in CH_2Cl_2 (20 ml) was added mCPBA (0.3 g, 70%, 1.2 mmol) in a portionwise manner at 0 °C. The mixture was brought to room temperature and the reaction mixture was stirred

for 20 hr under N_2. Na_2SO_3 (20 ml 1.0 M solution) was added to the reaction mixture at 0 °C to quench the reaction. The aqueous phase was extracted with CH_2Cl_2 (20 ml x 2). The combined organic phase was washed in turn with saturated $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave light brown solid residue. The crude products were purified by flash chromatography on silica gel (hexane/ethyl ether=9:1) to give 0.08 g (1S, 4S, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8a** (50.3%, $[\alpha]_D$=(-)60, c=1, MeOH) and 0.065 g **8b** (1R, 4S, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane (41%, $[\alpha]_D$=(-)76, c=1, MeOH).

(1S, 4S, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8a**:

^{1}HNMR ($CDCl_3$, 400MHz) 1.71(m, 1H, H-5) 1.89(m, 1H, H-5) 3.27(m, 1H, H-1) 3.34(m,1H, H-7) 3.82(d, J=9.6Hz, 1H, Ph2CH) 3.95(d, J=14Hz, 1H, H-2) 4.14(dt, J=2.4Hz, 10.2Hz, H-4) 4.22(dd, J=4Hz, 12.8Hz, 1H, H-2) 7.16-7.36(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 31.1 51.82 55.52 56.67 67.86 68.03 74.20 126.63 126.86 127.38 128.35 128.51 128.57 128.65 128.74 128.96 142.18 142.37

(1R, 4S, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane:

^{1}HNMR ($CDCl_3$, 400MHz) 1.66-1.86(m, 2H, H-5) 3.06(m, 1H, H-1) 3.28(m,1H, H-7) 3.78-3.98(m, 3H, Ph2CH, H-2, H-4) 4.19(d, J=13.6Hz, 1H, H-2) 7.16-7.36(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 31.1 51.82 55.52 56.67 67.86 68.03 74.20 126.63 126.86 127.38 128.35 128.51 128.57 128.65 128.74 128.96 142.18 142.37

Synthesis of (1R, 4R, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane (8c) and (1S, 4R, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane (8d)

(2R)-2-benzhydryl-3,6-dihydro-2H-pyran **7b** (0.2 g, 0.79 mmol) was reacted with mCPBA (0.27 g, 70%, 1.58 mmol) (Procedure D) to yield the corresponding (1R, 4R, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8c** 0.11 g (52%, $[\alpha]_D$=(+)60.4, c=1, MeOH)) and (1S, 4R, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8d** 0.086 g (41%, $[\alpha]_D$=(+)78, c=1, MeOH). The The ^{1}HNMR and ^{13}CNMR were identical for both (1S, 4S,

6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane and (1R, 4S, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane.

(1R, 4R, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8c**:

^{1}HNMR ($CDCl_3$, 400MHz) 1.71(m, 1H, H-5) 1.89(m, 1H, H-5) 3.27(m, 1H, H-1) 3.34(m,1H, H-7) 3.82(d, J=9.6Hz, 1H, Ph2CH) 3.95(d, J=14Hz, 1H, H-2) 4.14(dt, J=2.4Hz, 10.2Hz, H-4) 4.22(dd, J=4Hz, 12.8Hz, 1H, H-2) 7.16-7.36(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 31.1 51.82 55.52 56.67 67.86 68.03 74.20 126.63 126.86 127.38 128.35 128.51 128.57 128.65 128.74 128.96 142.18 142.37

(1S, 4R, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8d**:

^{1}HNMR ($CDCl_3$, 400MHz) 1.66-1.86(m, 2H, H-5) 3.06(m, 1H, H-1) 3.28(m,1H, H-7) 3.78-3.98(m, 3H, Ph2CH, H-2, H-4) 4.19(d, J=13.6Hz, 1H, H-2) 7.16-7.36(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 31.1 51.82 55.52 56.67 67.86 68.03 74.20 126.63 126.86 127.38 128.35 128.51 128.57 128.65 128.74 128.96 142.18 142.37

Procedure E. Synthesis of (2S, 4R, 5R)-2-benzhydryl-5-(4-methoxy-benzylamino)-tetrahydro-pyran-4-ol (-)9a

The mixture of (1S, 4S, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8a** (0.027 g, 0.10 mmol) and para-methoxy-benzylamine (0.28 g, 2.03 mmol) in ethanol (1 ml) was refluxed under N_2 overnight. The solvent was removed and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate/Et3N=6:4:0.2) to give (2S, 4R, 5R)-2-benzhydryl-5-(4-methoxy-benzylamino)-tetrahydro-pyran-4-ol, **(-)-9a,** 0.03 g (73.2%, $[\alpha]_D$=(-)71.9, c=1, MeOH)

^{1}HNMR ($CDCl_3$, 400MHz) 1.42(m,1H, H-3) 1.72(m, 3H, H-3, NH, OH) 2.44(m, 1H, H-5) 3.66(d, J=12.8Hz, H-6) 3.74-3.84(m, 5H, -OCH3, Ph-CH2) 3.87-3.98(m, 3H, H-4, H-6, Ph2CH) 4.50(dt, J=2.4Hz, 9.6Hz, 1H, H-2) 6.80-7.40(m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.69 51.04 55.51 56.71 56.79 65.08 67.82 73.81 114.03 126.55 126.75 128.61 128.87 129.47 142.18 142.37

Free base was converted into oxalate: mp °C Anal. [$C_{26}H_{29}NO_3 \bullet (COOH)_2$] C, H, N.

Synthesis of (2R, 4S, 5S)-2-benzhydryl-5-(4-methoxy-benzylamino)-tetrahydro-pyran-4-ol(+)9a

(1R, 4R, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8c** (0.02 g, 0.075 mmol) was reacted with para-methoxy-benzylamine (0.21 g, 1.50 mmol) in ethanol (Procedure E) to yield (2R, 4S, 5S)-2-benzhydryl-5-(4-methoxy-benzylamino)-tetrahydro-pyran-4-ol **(+)-9a** 0.024 g (80%, $[\alpha]_D$=(+)72.8, c=1, MeOH). The ^{1}HNMR and ^{13}CNMR were identical with (2S, 4R, 5R)-2-benzhydryl-5-(4-methoxy-benzylamino)-tetrahydro-pyran-4-ol.

^{1}HNMR ($CDCl_3$, 400MHz) 1.42(m,1H, H-3) 1.72(m, 3H, H-3, NH, OH) 2.44(m, 1H, H-5) 3.66(d, J=12.8Hz, H-6) 3.74-3.84(m, 5H, -OCH3, Ph-CH2) 3.87-3.98(m, 3H, H-4, H-6, Ph2CH) 4.50(dt, J=2.4Hz, 9.6Hz, 1H, H-2) 6.80-7.40(m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.69 51.04 55.51 56.71 56.79 65.08 67.82 73.81 114.03 126.55 126.75 128.61 128.87 129.47 142.18 142.37

Free base was converted into oxalate: mp °C Anal. [$C_{26}H_{29}NO_3 \bullet (COOH)_2\,0.5H_2O$] C, H, N.

Synthesis of (2R, 4S, 5S)-2-benzhydryl-5-benzylamino-tetrahydro-pyran-4-ol (+)9e

(1R, 4R, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8c** (0.022 g, 0.082 mmol) was reacted with benzylamine (0.18 g, 1.64 mmol) in ethanol (Procedure E) to yield (2R, 4S, 5S)-2-benzhydryl-5-benzylamino-tetrahydro-pyran-4-ol, **(+)-9e** 0.025 g (81%, $[\alpha]_D$=(+)53.7, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.43(m,1H, H-3) 1.62-1.80(m, 3H, H-3, NH, OH) 2.54(m, 1H, H-5) 3.73(d, J=13.6Hz, 1H, Ph-CH2) 3.79(m, 1H, H-6) 3.86-4.02(m, 4H, H-4, H-6, Ph2CH, Ph-CH2) 4.50(dt, J=2.4Hz, 9.6Hz, 1H, H-2) 7.00-7.40(m, 15H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.67 51.64 56.78 56.83 65.10 67.83 73.80 126.57 126.77 127.24 128.30 128.63 128.89 142.25 142.34

Free base was converted into oxalate: mp °C Anal. [$C_{25}H_{27}NO_2 \bullet (COOH)_2\,0.3H_2O$] C, H, N.

Synthesis of (3R, 4R, 6S)-6-benzhydryl-4-(4-methoxy-benzylamino)-tetrahydro-pyran-3-ol(-)9b

(1R, 4S, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]heptane **8b** (0.021 g, 0.079 mmol) was reacted with para-methoxy-benzylamine (0.22 g, 1.58 mmol) (Procedure E) to yield (3R, 4R, 6S)-6-benzhydryl-4-(4-methoxy-benzylamino)-tetrahydro-pyran-3-ol, **(-)-9b** 0.02 g (63%, $[\alpha]_D$=(-)63.75, c=1, MeOH)

^{1}HNMR ($CDCl_3$, 400MHz) 1.37 (m, 1H, H-5) 1.81 (m, 1H, H-5) 2.95 (m, 1H, H-4) 3.46 (m, 1H, H-3) 3.56-3.72 (m, 3H, H-2, PhCH2) 3.81 (s, 3H, -OCH3) 3.96 (d, J=9.6Hz, 1H, Ph2CH) 4.04 (dd, J=1.6Hz, 12Hz, 1H, H-2) 4.53 (dt, J=2.4Hz, 9.6Hz, 1H, H-6) 6.8-7.4 (m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 31.14 51.23 55.45 55.53 56.64 67.84 68.05 74.20 126.63 126.86 127.38 128.35 128.51 128.57 128.65 128.74 128.96 142.18 142.37

Free base was converted into oxalate: mp °C Anal. [$C_{26}H_{29}NO_3 \bullet (COOH)_2\ 0.2H_2O$] C, H, N.

Synthesis of (3S, 4S, 6R)-6-benzhydryl-4-(4-methoxy-benzylamino)-tetrahydro-pyran-3-ol (+)9b

(1S, 4R, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]heptane **8d** (0.02 g, 0.075 mmol) was reacted with para-methoxy-benzylamine (0.21 g, 1.50 mmol) (Procedure E) to yield (3S, 4S, 6R)-6-benzhydryl-4-(4-methoxy-benzylamino)-tetrahydro-pyran-3-ol, **(+)-9b,** 0.029 (94%, $[\alpha]_D$=(+)65, c=1, MeOH). The ^{1}HNMR and ^{13}CNMR were identical with (3R, 4R, 6S)-6-benzhydryl-4-(4-methoxy-benzylamino)-tetrahydro-pyran-3-ol.

^{1}HNMR ($CDCl_3$, 400MHz) 1.37 (m, 1H, H-5) 1.81 (m, 1H, H-5) 2.95 (m, 1H, H-4) 3.46 (m, 1H, H-3) 3.56-3.72 (m, 3H, H-2, PhCH2) 3.81 (s, 3H, -OCH3) 3.96 (d, J=9.6Hz, 1H, Ph2CH) 4.04 (dd, J=1.6Hz, 12Hz, 1H, H-2) 4.53 (dt, J=2.4Hz, 9.6Hz, 1H, H-6) 6.8-7.4 (m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 31.14 51.23 55.45 55.53 56.64 67.84 68.05 74.20 126.63 126.86 127.38 128.35 128.51 128.57 128.65 128.74 128.96 142.18 142.37

Free base was converted into oxalate: mp °C Anal. [$C_{26}H_{29}NO_3 \bullet (COOH)_2\ 0.2H_2O$] C, H, N.

Synthesis of (3S, 4S, 6R)-6-benzhydryl-4-benzylamino-tetrahydro-pyran-3-ol (+)9f

(1S, 4R, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]heptane **8d** (0.019 g, 0.071 mmol) was reacted with benzylamine (0.15 g, 1.43 mmol) (Procedure E) to yield (3S, 4S, 6R)-6-benzhydryl-4-benzylamino-tetrahydro-pyran-3-ol, **(+)-9f,** 0.023 (85%, $[\alpha]_D$=(+)70.1, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.38 (m, 1H, H-5) 1.81 (m, 1H, H-5) 2.96 (m, 1H, H-4) 3.48 (m, 1H, H-3) 3.62-3.78 (m, 3H, H-2, PhCH2) 3.96 (d, J=9.6Hz, 1H, Ph2CH) 4.05 (m, 1H, H-2) 4.54 (dt, J=2.4Hz, 9.6Hz, 1H, H-6) 7.0-7.4 (m, 15H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 31.10 51.82 55.52 56.66 67.86 68.03 74.20 126.63 126.86 127.38 128.35 128.51 128.57 128.65 128.74 128.96 142.18 142.37

Free base was converted into oxalate: mp °C Anal. [$C_{25}H_{27}NO_2 \bullet (COOH)_2\ 0.25H_2O$] C, H, N.

Synthesis of (2S, 4R, 5R)-2-benzhydryl-5-(4-fluoro-benzylamino)-tetrahydro-pyran-4-ol (-)9c

(1S, 4S, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8a** (0.025 g, 0.094 mmol) was reacted with para-fluoro-benzylamine (0.24 g, 1.88 mmol) in ethanol (Procedure E) to yield (2S, 4R, 5R)-2-benzhydryl-5-(4-fluoro-benzylamino)-tetrahydro-pyran-4-ol, **(-)-9c,** 0.032 g (86%, $[\alpha]_D$=(-)77.2, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.40(m, 1H, H-3) 1.71(m, 1H, H-3) 1.78(bs, 2H, NH, OH) 2.41(m, 1H, H-5) 3.66(d, J=13.2Hz, 1H, H-6) 3.72-3.96(m, 5H, H-4, H-6, Ph2CH, PhCH2) 4.49(dt, J=2.4Hz, 10.4Hz, 1H, H-2) 6.8-7.4(m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.69 50.85 56.70 56.85 65.05 67.70 73.80 115.29 115.50 126.57 126.77 128.61 128.64 128.86 129.74 129.83 142.19 142.31

Free base was converted into oxalate: mp °C Anal. [$C_{25}H_{26}NFO_2 \bullet (COOH)_2$] C, H, N.

Synthesis of (2R, 4S, 5S)-2-benzhydryl-5-(4-fluoro-benzylamino)-tetrahydro-pyran-4-ol (+)9c

(1R, 4R, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane, **8c,** (0.02 g, 0.075 mmol) was reacted with para-fluoro-benzylamine (0.19 g, 1.50 mmol) in ethanol (Procedure E) to yield (2R, 4S, 5S)-2-benzhydryl-5-(4-fluoro-benzylamino)-tetrahydro-pyran-4-ol, **(+)-9c,** 0.028 g (94%, $[\alpha]_D$=(+)77.6, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.43(m, 1H, H-3) 1.68-1.78(m, 3H, H-3, NH, OH) 2.43(m, 1H, H-5) 3.68(d, J=13.2Hz, 1H, H-6) 3.74-4.00(m, 5H, H-4, H-6, Ph2CH, PhCH2) 4.50(dt, J=2.4Hz, 10.4Hz, 1H, H-2) 6.8-7.4(m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.71 50.87 56.72 56.85 65.06 67.75 73.81 115.30 115.51 126.57 126.78 128.61 128.65 128.87 129.75 129.83 142.20 142.31

Free base was converted into oxalate: mp °C Anal. [$C_{25}H_{26}NFO_2 \bullet (COOH)_2\ 0.2H_2O$] C, H, N

Synthesis of (2S, 4R, 5R)-2-benzhydryl-5-[2-(4-fluoro-phenyl)-ethylamino]-tetrahydro-pyran-4-ol (-)9d

(1S, 4S, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8a** (0.025 g, 0.094 mmol) was reacted with 2-(4-fluoro-phenyl)-ethylamine (0.26 g, 1.88 mmol) in ethanol (Procedure E) to yield (2S, 4R, 5R)-2-benzhydryl-5-[2-(4-fluoro-phenyl)-ethylamino]-tetrahydro-pyran-4-ol, **(-)-9d,** 0.04 g (98%, $[\alpha]_D$=(-)62.9, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.40(m, 1H, H-3) 1.63(m, 1H, H-3) 1.84(s, 2H, NH, OH) 2.43(m, 1H, H-5) 2.73, 2.92(m, 4H, (F)PhCH2CH2) 3.70(dd, J=2Hz, 11.6Hz, 1H, H-6) 3.86-3.98(m, 3H, H-4, H-6, Ph2CH) 4.49(dt, J=2.4Hz, 10Hz, 1H, H-2) 6.8-7.4(m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.70 36.19 49.28 56.74 57.66 65.21 67.35 73.81 115.34 115.55 126.58 126.79 128.61 128.88 130.20 130.30 142.18 142.30

Free base was converted into oxalate: mp °C Anal. [$C_{26}H_{28}NFO_2 \bullet (COOH)_2\ 0.1H_2O$] C, H, N.

Synthesis of (2R, 4S, 5S)-2-benzhydryl-5-[2-(4-fluoro-phenyl)-ethylamino]-tetrahydro-pyran-4-ol (+)9d

(1R, 4R, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8c** (0.02 g, 0.075 mmol) was reacted with 2-(4-fluoro-phenyl)-ethylamine (0.21 g, 1.50 mmol) in ethanol (Procedure E) to yield (2R, 4S, 5S)-2-benzhydryl-5-[2-(4-fluoro-phenyl)-ethylamino]-tetrahydro-pyran-4-ol, **(+)-9d**, 0.030 g (98%, $[\alpha]_D$=(+)63.4, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.40(m, 1H, H-3) 1.63(m, 1H, H-3) 1.84(s, 2H, NH, OH) 2.43(m, 1H, H-5) 2.73, 2.92(m, 4H, (F)PhCH2CH2) 3.70(dd, J=2Hz, 11.6Hz, 1H, H-6) 3.86-3.98(m, 3H, H-4, H-6, Ph2CH) 4.49(dt, J=2.4Hz, 10Hz, 1H, H-2) 6.8-7.4(m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.72 36.26 49.33 56.74 57.67 65.28 67.47 73.80 115.33 115.53 126.57 126.78 128.61 128.88 130.22 130.30 142.19 142.30

Free base was converted into oxalate: mp °C Anal. [$C_{26}H_{28}NFO_2 \bullet (COOH)_2\ 0.5H_2O$] C, H, N.

Procedure F. Synthesis of (2S, 4R, 5R)-5-Azido-2-benzhydryl-tetrahydro-pyran-4-ol (10a)

A solution of (1S, 4S, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8a** (0.05 g, 0.19 mmol) in a 8:1 MeOH/H_2O (2 ml) mixture was treated with NaN_3 (0.061 g, 0.94 mmol) and NH_4Cl (0.022 g, 0.41 mmol) and the resulting reaction mixture was stirred at 80 °C overnight. The reaction mixture was diluted with ether and and the organic layer was separated. Evaporation of the washed (saturated aqueous $NaHCO_3$ and water) ether extracts afforded a crude solid product. Purification of the product by flash chromatography (Hexane/Ethyl Acetate=4:1) yielded (2S, 4R, 5R)-5-Azido-2-benzhydryl-tetrahydro-pyran-4-ol **10a** 0.05 g (95%, $[\alpha]_D$=(-)109.3, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.44(m, 1H, H-3) 1.79(m, 1H, H-3) 1.91(s, 1H, OH) 3.258(m, 1H, H-5) 3.82-4.04(m, 4H, H-4, H-6, Ph2CH) 4.49(dt, J=2.4Hz, 10Hz, 1H, H-2) 7.0-7.4(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.56 56.96 59.63 64.81 66.32 73.56 126.64 126.88 128.62 128.64 128.67 128.92 142.04

Synthesis of (2R, 4S, 5S)-5-Azido-2-benzhydryl-tetrahydro-pyran-4-ol (10b)

(1R, 4R, 7S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8c** (0.04 g, 0.15 mmol) was treated with NaN_3 (0.05 g, 0.75 mmol) and NH_4Cl (0.018 g, 0.33 mmol) (Procedure F) yielded (2R, 4S, 5S)-5-Azido-2-benzhydryl-tetrahydro-pyran-4-ol **10b**, 0.04 g (95%, $[\alpha]_D$=(+)108, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.45(m, 1H, H-3) 1.80(m, 1H, H-3) 1.91(s, 1H, OH) 3.27(m, 1H, H-5) 3.84-4.05(m, 4H, H-4, H-6, Ph2CH) 4.50(dt, J=2.4Hz, 10Hz, 1H, H-2) 7.0-7.4(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.59 56.96 59.64 64.81 66.35 73.56 126.64 126.87 128.62 128.64 128.67 128.92 142.06

Procedure G. Synthesis of (2S, 4R, 5R)-5-Amino-2-benzhydryl-tetrahydro-pyran-4-ol (11a)

(2S, 4R, 5R)-5-Azido-2-benzhydryl-tetrahydro-pyran-4-ol (0.05 g, 0.18 mmol) dissolved in methanol (20 ml) was hydrogenated in the presence of 10% Pd/C (0.006 g). The mixture was filtered through a short bed of cellite, and evaporation of the solvent gave (2S, 4R, 5R)-5-amino-2-benzhydryl-tetrahydro-pyran-4-ol 0.05 g (97%, $[\alpha]_D$=(-)66, c=1, MeOH), which was pure enough for the next reaction.

^{1}HNMR ($CDCl_3$, 400MHz) 1.40(m, 1H, H-3) 1.70(m, 1H, H-3) 2.73(s, 1H, H-5) 3.20(m, 3H, NH, OH) 3.60(m, 1H, H-6) 3.8-4.0(m, 3H, H-4, H-6, Ph2CH) 4.46(t, J=10Hz, 1H, H-2) 7.0-7.4(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 32.87 51.26 56.68 67.25 67.85 74.15 126.60 126.82 128.61 128.65 128.89 142.15 142.18

Synthesis of (2R, 4S, 5S)-5-Amino-2-benzhydryl-tetrahydro-pyran-4-ol (11b)

(2R, 4S, 5S)-5-Azido-2-benzhydryl-tetrahydro-pyran-4-ol (0.05 g, 0.14 mmol) was hydrogenated (Procedure G) to yield (2R, 4S, 5S)-5-amino-2-benzhydryl-tetrahydro-pyran-4-ol 0.04 g (97%, $[\alpha]_D$=(+)66.2, c=1, MeOH).

^{1}HNMR (CD3OD, 400MHz) 1.43(m, 1H, H-3) 1.72(m, 1H, H-3) 2.65(m, 1H, H-5) 3.57(m, 1H, H-6) 3.82(m, 1H, H-4) 3.92-4.0(m, 2H, H-6, Ph2CH) 4.52(dt, J=2Hz, 10.4Hz, 1H, H-2) 7.0-7.4(m, 10H, aromatic-CH)

^{13}CNMR (CD3OD, 100MHz) 32.40 50.67 56.92 66.65 67.47 74.04 125.96 126.35 128.01 128.38 128.42 142.44 142.77

Procedure H. Synthesis of (2S, 4R, 5R)-2-benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol (-)12

Into a solution of (2S, 4R, 5R)-5-amino-2-benzhydryl-tetrahydro-pyran-4-ol **11a** (0.02 g, 0.09 mmol), 4-hydroxybenzaldehyde (0.01 g, 0.09 mmol) and glacial acetic acid (0.005 g, 0.09 mmol) in 1,2-dichloroethane (5 ml) was added portionwise $NaCNBH_3$ (0.007 g, 0.11 mmol) in methanol (1 ml). The reaction was continued for 4 hr. Water was added to quench the reaction and the mixture was stirred for 30 minutes at 0°C. he reaction mixture was stirred with saturated aqueous $NaHCO_3$ and the product was extracted with methylene chloride (3 × 10 ml). The combined organic phase was washed with brine, water and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography (Hexane/Ethyl Acetate/Triethylamine 3:2:0.2) to give (2S, 4R, 5R)-2-benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol, **(-)-12,** 0.03 g (80%, $[\alpha]_D$=(-)72.6, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.40(m, 1H, H-3) 1.66(m, 1H, H-3) 2.45(s, 1H, H-5) 3.23(bs, NH, OH) 3.58(d, J=12.4Hz, 1H, (OH)PhCH2) 3.7-3.8(m, 2H, H-6, (OH)PhCH2) 3.84-4.0(m, 3H, H-4, H-6, Ph2CH) 4.49(dt, J=2Hz, 10Hz, 1H, H-2) 6.57, 7.03, 7.1-7.36(m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.56 50.86 56.49 56.60 64.55 67.19 73.95 115.82 126.61 126.79 128.59 128.64 128.68 128.87 129.91 130.87 142.09 142.22 155.61

Free base was converted into oxalate: mp °C Anal. [$C_{25}H_{27}NO_3 \bullet (COOH)_2\ 0.4H_2O$] C, H, N.

Synthesis of (2R, 4S, 5S)-2-benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol (+)12

(2R, 4S, 5S)-5-amino-2-benzhydryl-tetrahydro-pyran-4-ol **11b** (0.02 g, 0.07 mmol) was reacted with 4-hydroxybenzaldehyde (0.009 g, 0.071 mmol),glacial acetic acid (0.004 g, 0.071 mmol) and $NaCNBH_3$ (0.005 g, 0.085 mmol) (Procedure H) to give (2R, 4S, 5S)-2-benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol, **(+)-12**, 0.023 g (85%, $[\alpha]_D$=(+)72.4, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.42(m, 1H, H-3) 1.68(m, 1H, H-3) 2.46(m, 1H, H-5) 3.52(bs, NH, OH) 3.60(d, J=13.6Hz, 1H, (OH)PhCH2) 3.72-3.82(m, 2H, H-6, (OH)PhCH2) 3.86-4.0(m, 3H, H-4, H-6, Ph2CH) 4.50(dt, J=2.4Hz, 10.4Hz, 1H, H-2) 6.58, 7.05, 7.1-7.36(m, 14H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 33.62 50.94 56.59 64.64 67.36 73.93 115.78 126.62 126.79 128.59 128.64 128.69 128.88 129.87 142.08 142.23 155.51

Free base was converted into oxalate: mp °C Anal. [$C_{25}H_{27}NO_3 \bullet (COOH)_2\ 0.4H_2O$] C, H, N.

Procedure I. Synthesis of (3R, 6S)-6-benzhydryl-tetrahydro-pyran-3-ol (13a)

(1S, 4S, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane **8a** (0.3 g, 1.13 mmol) in dry pentane (10 ml) was added to the suspension of $LiAlH_4$ (0.21 g, 5.64 mmol) in dry pentane (20 ml). The resulting reaction mixture was stirred under N_2 for 20 hr at room temperature. The reaction was next quenched with 10% NaOH, diluted with ethyl acetate (30 ml), and the precipitate was removed by filtration. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by flash chromatography of

the crude product produced pure (3R, 6S)-6-benzhydryl-tetrahydro-pyran-3-ol, **13a,** 0.23 g (75%, $[\alpha]_D$=(-)-61.6, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.40(m, 2H, H-5) 1.58(m, 1H, H-4) 2.07(m, 1H, H-4) 3.14(t, J=10.4Hz, 1H, H-2) 3.69(m, 1H, H-3) 3.82-4.04(m, 3H, H-2, H-6, Ph_2CH) 7.1-7.4(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 29.47 33.18 57.40 66.55 73.12 78.95 126.51 126.74 128.54 128.60 128.79 142.41 142.77

Synthesis of (3S, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol (13b)

(1R, 4R, 6S)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]-heptane (0.05 g, 0.19 mmol) was treated with LiAlH4 (0.036 g, 0.94 mmol) (Procedure I) in dry pentane to yield trans-(3S, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol 0.035 g (70%, $[\alpha]_D$=(+)61.7, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.40 (m, 2H, H-5), 1.58 (m, 1H, H-4), 2.07 (m, 1H, H-4), 3.14 (t, J=10.4Hz, 1H, H-2), 3.69 (m, 1H, H-3), 3.82-4.04 (m, 3H, H-2, H-6, Ph_2CH), 7.1-7.4 (m, 10H, aromatic-CH).

^{13}CNMR ($CDCl_3$, 100MHz) 29.47 33.18 57.40 66.55 73.12 78.95 126.51 126.74 128.54 128.60 128.79 142.41 142.77

An Alternative Procedure for the synthesis of (3S, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol (13b)

Synthesis of (3R, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol (18)

Treatment of (1S, 4R, 6R)-4-benzhydryl-3,7-dioxa-bicyclo[4.1.0]heptane **8d** (0.06 g, 0.23 mmol) with a suspension of LiAlH4 (0.06 g, 1.58 mmol) in pentane along with with 12-crown-4 ether (0.31 g, 1.74 mmol) for 15 h at room temperature afforded (3R, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol **18** 0.046 g (77%, $[\alpha]_D$=(+)74.9, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.28(m, 1H, H-5) 1.58-1.74(m, 2H, H-4, H-5) 1.88(m, 1H, H-5) 2.20(bs,1H, OH) 3.63(m, 1H, H-2) 3.75(bs, 1H, H-3) 3.88-4.10(m, 3H, H-2, H-6, Ph_2CH) 7.1-7.4(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 24.95 30.15 57.78 64.77 73.02 79.64 126.56 126.77 128.58 128.69 128.71 128.81 142.30 142.42.

Procedure J. Synthesis of methanesulfonic acid *cis*-(3R, 6R)-6-benzhydryl-tetra-hydropyran-3-yl ester (19)

Methanesulfonyl chloride (0.067 g, 0.58 mmol) was reacted with cis-(3R, 6R)-6-diphenylmethyl-tetrahydropyran-3-ol **18** (0.078 g, 0.29 mmol) in the presence of triethylamine (0.044 g, 0.44 mmol) in dry methylene chloride (10 ml) to give cis-(3R, 6R)-6-diphenylmethyl tetrahydropyran-3-yl methanesulfonate **19** 0.1 g (quantitative yield, $[\alpha]_D$=(+)65.7, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.46(m, 1H, H-5) 1.62-1.78(m, 2H, H-4, H-5) 2.24(m, 1H, H-5) 2.96(s, 3H, CH_3SO_2) 3.36(t, J=10.4 Hz, 1H, H-2) 3.88(d, J=8.8 Hz, 1H, Ph_2CH) 4.0(dt, J=2 Hz, 8.8 Hz, 1H, H-2) 4.14(m, 1H, H-2) 4.61(m, 1H, H-3) 7.1-7.4(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 29.49 30.58 38.71 57.10 69.87 75.23 79.07 126.69 126.93 128.57 128.60 128.67 128.89 141.94 142.33

Synthesis of (3S, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol (13b)

cis-(3R, 6R)-6-diphenylmethyl tetrahydropyran-3-yl methanesulfonate **19** (0.1 g, 0.29 mmol) and 18-crown-6 (0.76 g, 2.9 mmol) are dissolved in a 1:1 mixture of DMSO and DMF (15 ml). KO2 (0.062 g, 0.87 mmol) was added and the solution was stirred under N_2. After 5 hr, the reaction was over. H2O (1 ml) and a few drops of 1M solution of HCl were added and the solution was extracted with Et2O (3 X 10 ml). The ether phase was washed with water and saturated brine, dried over anhydrous Na2SO4 and evaporated to dryness. The crude product was chromatographed on silica gel using hexane/ethyl acetate 1:1 tp yield pure trans-(3S, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol **13b** 0.062 g (80%, $[\alpha]_D$=(+)62.8, c=1, MeOH).

^{1}HNMR ($CDCl_3$, 400MHz) 1.40(m, 2H, H-5) 1.58(m, 1H, H-4) 2.07(m, 1H, H-4) 3.14(t, J=10.4Hz, 1H, H-2) 3.69(m, 1H, H-3) 3.82-4.04(m, 3H, H-2, H-6, Ph_2CH) 7.1-7.4(m, 10H, aromatic-CH)

^{13}CNMR ($CDCl_3$, 100MHz) 29.47 33.18 57.40 66.55 73.12 78.95 126.51 126.74 128.54 128.60 128.79 142.41 142.77

Synthesis of methanesulfonic acid *trans*-(3R, 6S)-6-benzhydryl-tetra-hydropyran-3-yl ester (14a)

Methanesulfonyl chloride (0.20 g, 1.7 mmol) was reacted with *trans*-(3R, 6S)-6-diphenylmethyl-tetrahydropyran-3-ol **13a** (0.23 g, 0.85 mmol) (Procedure J) to give *trans*-(3R, 6S)-6-diphenylmethyl tetrahydropyran-3-yl methanesulfonate **14a** 0.23 g (80%, $[\alpha]_D$=(-)54, c=1, MeOH).

.^{1}H NMR(400MHz, $CDCl_3$) 1.47(m, 1H, H-5) 1.62-1.80(m, 2H, H-5, H-4) 2.25(m, 1H, H-4) 2.98(s, 3H, CH_3SO_2) 3.37(t, J=10.4Hz, 1H, H-2ax) 3.89(d, J=8.8Hz, 1H, Ph2CH) 4.01(dt, J=2Hz, 9.6Hz, 1H, H-6) 4.15(m, 1H, H-2eq) 4.62(m, 1H, H-3) 7.16-7.38(m, 10H, aromatic-CH).

^{13}C NMR(100MHz, $CDCl_3$) δ(ppm) 29.46, 30.57, 38.71, 57.07, 69.85, 75.19, 79.04, 126.67, 126.90, 128.54, 128.57, 128.63, 128.86, 141.87, 142.28

Synthesis of 14b

Synthesis of methanesulfonic acid trans-(3S, 6R)-6-benzhydryl-tetra-hydropyran-3-yl ester 14b

Trans-(3S, 6R)-6-benzhydryl-tetrahydro-pyran-3-ol (0.025 g, 0.093 mmol) was reacted with methanesulfonyl chloride (0.021 g, 0.19 mmol) (Procedure J) to yield trans-(3S, 6R)-6-benzhydryl-tetra-hydropyran-3-yl ester **14b** 0.028 g (88%, $[\alpha]_D$=(+)54.8, c=1, MeOH).

.^{1}H NMR(400MHz, $CDCl_3$) 1.47(m, 1H, H-5) 1.62-1.80(m, 2H, H-5, H-4) 2.25(m, 1H, H-4) 2.98(s, 3H, CH_3SO_2) 3.37(t, J=10.4Hz, 1H, H-2ax) 3.89(d, J=8.8Hz, 1H, Ph2CH) 4.01(dt, J=2Hz, 9.6Hz, 1H, H-6) 4.15(m, 1H, H-2eq) 4.62(m, 1H, H-3) 7.16-7.38(m, 10H, aromatic-CH).

^{13}C NMR(100MHz, $CDCl_3$) δ(ppm) 29.46, 30.57, 38.71, 57.07, 69.85, 75.19, 79.04, 126.67, 126.90, 128.54, 128.57, 128.63, 128.86, 141.87, 142.28

Procedure K. Synthesis of *Cis*-(3S, 6S)-3-azido-6-benzhydryl-tetrahydropyran

15a*Trans*-(3R, 6S)-6-Diphenylmethyl-tetrahydropyran-3-yl methanesulfonate **14a** (0.23 g, 0.68 mmol) in dry DMF (10 ml) was reacted with sodium azide (0.13 g, 2.03 mmol) to yield *cis*-(3S, 6S)-3-azido-6-diphenylmethyl-tetrahydropyran, **15a,** 0.17 g (86%, $[\alpha]_D$=(-)78.2, c=1, MeOH).

^{1}H NMR (400MHz, $CDCl_3$) 1.38 (m, 1H, H-5) 1.60-1.84 (m, 2H, H-5, H-4) 1.98 (m, 1H, H-4), 3.55 (m, 1H, H-3), 3.63 (dd, J=2Hz, 12.4Hz, 1H, H-2) 3.98-4.12(m, 3H, H-2, H-6, Ph_2CH) 7.16-7.40(m, 10H, aromatic-CH)

^{13}C NMR(100MHz, $CDCl_3$) 25.47, 27.70, 55.60, 57.58, 69.79, 79.48, 126.58, 126.84, 128.59, 128.69, 128.76, 128.86 142.28 142.29

Procedure L. Synthesis of *Cis*-(3S, 6S)-(6-benzhydryl-tetrahydropyran-3-yl)-amine (16a)

Cis-(3S, 6S)-3-azido-6-diphenylmethyl-tetrahydropyran **15a** (0.17 g, 0.58 mmol) in methanol (25 ml) was hydrogenated under the catalyst of 10% Pd-C (0.017 g, 10% wt) for 4 hr to give *cis*-(3S, 6S)-(6-diphenylmethyl-tetrahydropyran-3-yl)-amine **16a,** 0.12 g (78%, $[\alpha]_D$=(-)74.3, c=1, MeOH).

^{1}H NMR(400MHz, CD_3OD) 1.27(m, 1H, H-5) 1.52(m, 1H, H-5) 1.62-1.80(m, 2H, H-4) 2.78(bs, 1H, H-3) 3.63(m, 2H, H-2) 3.95(d, J=8.8Hz, 1H, Ph_2CH) 4.10(dt, J=2Hz, 9.6Hz, 1H, H-6) 7.0-7.40(m, 10H, aromatic-CH).

^{13}C NMR(100MHz, $CDCl_3$) 24.47, 29.29, 45.15, 57.32, 72.08, 79.28, 125.97, 126.34, 128.02, 128.39, 128.42 128.54 142.72 142.82

Synthesis of *Cis*-(3R, 6R)-(6-benzhydryl-tetrahydropyran-3-yl)-amine (14b)

Synthesis of *Cis*-(3R, 6R)-3-azido-6-benzhydryl-tetrahydropyran

trans-(3S, 6R)-6-Diphenylmethyl-tetrahydropyran-3-yl methanesulfonate (0.028 g, 0.082 mmol) was reacted with NaN3 (0.016 g, 0.25 mmol) (Procedure L) to yield *cis*-(3R, 6R)-3-azido-6-benzhydryl-tetrahydropyran 0.024 g (quantitative yield, $[\alpha]_D$=(+)77.6, c=1, MeOH).

^{1}H NMR (400MHz, $CDCl_3$) 1.38 (m, 1H, H-5) 1.60-1.84 (m, 2H, H-5, H-4) 1.98 (m, 1H, H-

4), 3.55 (m, 1H, H-3), 3.63 (dd, J=2Hz, 12.4Hz, 1H, H-2) 3.98-4.12(m, 3H, H-2, H-6, Ph_2CH) 7.16-7.40(m, 10H, aromatic-CH)

^{13}C NMR(100MHz, $CDCl_3$) 25.47, 27.70, 55.60, 57.58, 69.79, 79.48, 126.58, 126.84, 128.59, 128.69, 128.76, 128.86 142.28 142.29

Cis-(3R, 6R)-3-azido-6-diphenylmethyl-tetrahydropyran (0.024 g, 0.082 mmol) was hydrogenated (Procedure M) to yield *cis*-(3R, 6R)-(6-benzhydryl-tetrahydropyran-3-yl)-amine **14b** 0.02 g (92%, $[\alpha]_D$=(+)74.0, c=1, MeOH).

^1H NMR(400MHz, CD_3OD) 1.27(m, 1H, H-5) 1.52(m, 1H, H-5) 1.62-1.80(m, 2H, H-4) 2.78(bs, bs, 1H, H-3) 3.63(m, 2H, H-2) 3.95(d, J=8.8Hz, 1H, Ph_2CH) 4.10(dt, J=2Hz, 9.6Hz, 1H, H-6) 7.0-7.40(m, 10H, aromatic-CH).

^{13}C NMR(100MHz, $CDCl_3$) 24.47, 29.29, 45.15, 57.32, 72.08, 79.28, 125.97, 126.34, 128.02, 128.39, 128.42 128.54 142.72 142.82

Syntheis of *cis*-(3S, 6S)-(6-benzhydryl-tetrahydropyran-3-yl)-(4-hydroxy-benzyl)-amine (-)17

cis-(3S, 6S)-3-amino-6-diphenylmethyl pyran **16a** (0.02 g, 0.075 mmol) was reacted with 4-hydroxybenzaldehyde (0.009 g, 0.075 mmol) in the presence of glacial acetic acid (0.005 g, 0.075 mmol) in 1,2-dichloroethane (10 ml), then was reduced by $NaCNBH_3$ (0.0057 g, 0.09 mmol) (Procedure H) to give *cis*-(3S, 6S)-(6-benzhydryl-tetrahydro-pyran-3-yl)-(4-flurobenzyl)-amine **(-)-17,** 0.02 g (72%, $[\alpha]_D$=(-) 38.3, c=1, MeOH).

^1H NMR (400MHz, $CDCl_3$) 1.36(m, 1H, H-5) 1.51(m, 1H, H-5) 1.68(m, 1H, H-4) 2.0(m, 1H, H-4) 2.71(s, 1H, H-3) 3.56(dd, J=1.6Hz, 11.6Hz, 1H, H-2) 3.64(m, 2H, (HO)Ph-CH_2) 3.96(d, J=8.4Hz, 1H, Ph_2CH) 4.02-4.16(m, 2H, H-6, H-2) 6.52(m, 2H, aromatic-CH) 6.98-7.38(m, 12H, aromatic-CH).

^{13}C NMR (100MHz, $CDCl_3$) 25.28 27.31 50.39 50.68 57.21 69.88 79.45 116.04 126.56 126.67 128.54 128.70 128.73 128.93 129.86 130.47 142.16 142.58 155.93

Free base was converted into oxalate: mp 136-138 °C Anal. [$C_{25}H_{27}NO_2 \bullet (COOH)_2$ $0.6H_2O$] C, H, N.

Syntheis of *cis*-(3R, 6R)-(6-benzhydryl-tetrahydropyran-3-yl)-(4-hydroxy-benzyl)-amine (+)17

cis-(3R, 6R)-3-amino-6-diphenylmethyl pyran **14b** (0.024 g, 0.09 mmol) was reacted with 4-hydroxybenzaldehyde (0.011 g, 0.09 mmol) in the presence of glacial acetic acid (0.0054 g, 0.09 mmol) in 1,2-dichloroethane (10 ml), then was reduced by $NaCNBH_3$ (0.012 g, 0.18 mmol) (Procedure H) to give *cis*-(3R, 6R)-(6-benzhydryl-tetrahydro-pyran-3-yl)-(4-flurobenzyl)-amine 0.024 g (71%, $[\alpha]_D$=(+) 40.1, c=1, MeOH).

^1H NMR (400MHz, $CDCl_3$) 1.34(m, 1H, H-5) 1.51(m, 1H, H-5) 1.65(m, 1H, H-4) 1.96(m, 1H, H-4) 2.67(m, 1H, H-3) 3.56(dd, J=1.6Hz, 11.6Hz, 1H, H-2) 3.66(m, 2H, (HO)Ph-CH_2) 3.96(d, J=8.8Hz, 1H, Ph_2CH) 3.98-4.12(m, 2H, H-6, H-2) 6.65(m, 2H, aromatic-CH) 7.06-7.38(m, 12H, aromatic-CH).

^{13}C NMR (100MHz, $CDCl_3$) 25.28 27.31 50.39 50.68 57.21 69.88 79.45 116.04 126.56 126.67 128.54 128.70 128.73 128.93 129.86 130.47 142.16 142.58 155.93

Free base was converted into oxalate: mp 136-138 °C Anal. [$C_{25}H_{27}NO_2 \bullet (COOH)_2$ $1.8H_2O$] C, H, N.

Table 1. Affinity of Drugs at Dopamine, Serotonin, and Norepinephrine Transporters in Rat Striatum.

compd	DAT uptake, IC_{50}, nM, [^{3}H]DA [a]	SERT uptake, IC_{50}, nM, [^{3}H]5-HT[a]	NET uptake, IC_{50}, nM [^{3}H]NE[a]
Cocaine			
GBR 12909			
(+)-9a	148 ± 22	745 ± 30	445 ± 39
(+)-9b	2667 ± 260	3809 ± 460	1841 ± 580
(+)-9c	440 ± 30	5563 ± 640	1132 ± 580
(+)-9d	218 ± 20	2947 ± 380	77.3 ± 3

(+)-9e	341 ± 43	6121 ± 729	770 ± 33
(+)-9f	962 ± 97	4423 ± 409	3219 ± 571
(-)-9a	155 ± 16	28.9 ± 4.1	17.7 ± 5.9
(-)-9b	822 ± 126	1067 ± 94	765 ± 34
(-)-9c	169 ± 20	1460 ± 122	13.27 ± 1.05
(-)-9d	427 ± 67	3573 ± 143	439 ± 14
(-)-9e			
(+)-12	123 ± 10	2833 ± 480	102 ± 20
(-)-12	232 ± 28	265 ± 14	11.22 ± 1.01
(+)-17	90.7 ± 4	209 ± 25	45.6 ± 6
(-)-17	114 ± 8	42 ± 3	5.5 ± 0.1

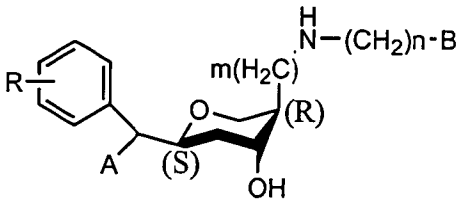
Elemental Analysis Results of the Final Products:

compound	Calculated			Found		
	C	H	N	C	H	N
(+) 9a 0.5H_2O	66.91	6.42	2.79	66.74	6.40	2.79
(-) 9a	68.14	6.33	2.84	67.94	6.49	2.70
(+) 9b 0.2H_2O	67.64	6.37	2.82	67.60	6.37	2.75
(-) 9b 0.2H_2O	67.64	6.37	2.82	67.50	6.30	2.80
(+) 9c 0.2H_2O	66.84	5.90	2.89	66.83	6.01	2.83
(-) 9c	67.35	5.86	2.91	67.05	5.92	2.78
(+) 9d 0.5H_2O	66.65	6.19	2.78	66.44	6.05	2.82
(-) 9d 0.1H_2O	67.62	6.12	2.82	67.49	6.00	2.79
(+) 9e 0.3H_2O	69.15	6.36	2.98	69.15	6.45	2.88
(+) 9f 0.25H_2O	69.28	6.35	2.99	69.13	6.55	2.83
(+) 12 0.4H_2O	66.62	6.17	2.87	66.32	6.18	2.71
(-) 12 0.4H_2O	66.62	6.17	2.87	66.85	6.18	2.65

(+) 16 1.8H_2O	65.38	6.63	2.82	65.39	6.23	2.71
(-) 16 0.6H_2O	68.37	6.42	2.95	68.07	6.33	2.93

The following subject matter, which may appear to be in claim-like form, is not intended to specify every aspect of the invention disclosed in this provisional application to which the inventor herein may be entitled.

Figure 1



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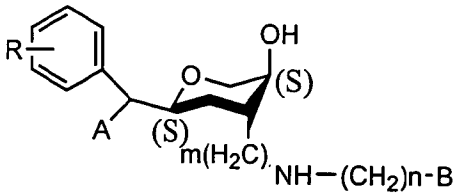

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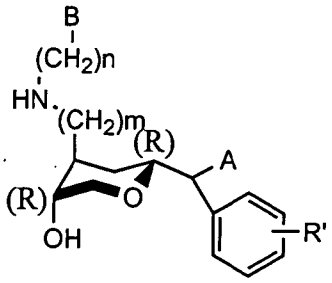
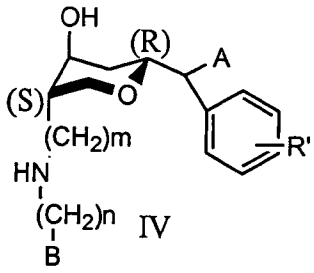


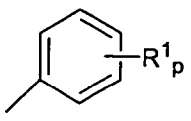
III

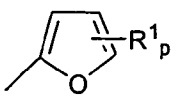


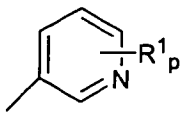
IV

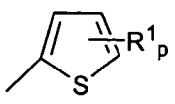
Compounds of Figure 1 preferably having the following structural variations

wherein A is

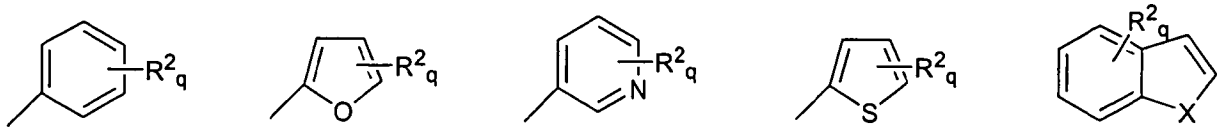








and B is



and where

n is 0,1,2,3,4

m is 0,1,2,3,4

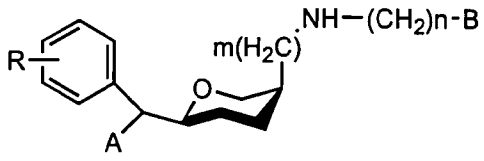
p is 0, 1, 2, 3, 4

q is 0, 1, 2, 3, 4, 5, 6, 7, 8

X is NH, O, S

R, R^1 and R^2 are selected from the group consisting of H, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} halogenated alkynyl, C_{2-6} hydroxy alkynyl, F, Cl, Br, I, CN, COOEt, OH, NO2, NH2, OR^3, wherein R^3 is C_{1-8} alkyl, C_{5-6} cycloalkyl, or C_{2-8} alkenyl or R^2 is a 5 or 6 membered heterocycle.and where any carbon of $-(CH_2)_n-$ may be substituted by OR^4 where R^4 is C_{1-8} alkyl or C_{2-18} alkylene, or $-COOR^5$ where R^5 is C_{1-18} alkyl or C_{2-18} alkylene.

Figure 2



V

Compounds of Figure 2 preferably having the following structural variations

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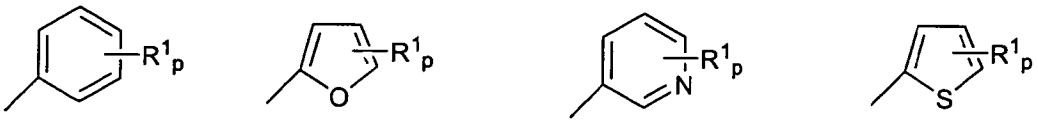
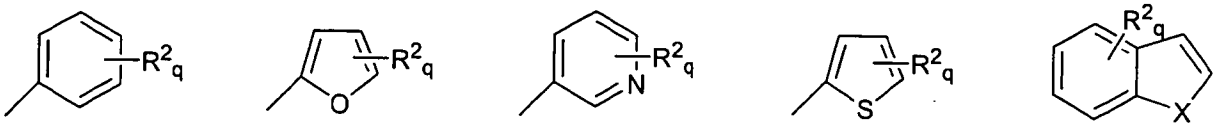


and B is



and where

n is 0, 1,2,3,4

m is 0, 1, 2, 3, 4

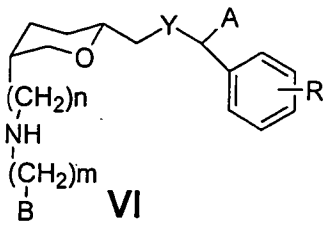
p is 0, 1, 2, 3, 4

q is 0, 1, 2, 3, 4, 5, 6, 7, 8

X is NH, O, S

R, R^1 and R^2 are selected from the group consisting of H, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} halogenated alkynyl, C_{2-6} hydroxy alkynyl, F, Cl, Br, I, CN, COOEt, OH, NO2, NH2, OR^3, wherein R^3 is C_{1-8} alkyl, C_{5-6} cycloalkyl, or C_{2-8} alkenyl or R^2 is a 5 or 6 membered heterocycle.and where any carbon of $-(CH_2)_n-$ may be substituted by OR^4 where R^4 is C_{1-8} alkyl or C_{2-18} alkylene, or $-COOR^5$ where R^5 is C_{1-18} alkyl or C_{2-18} alkylene.

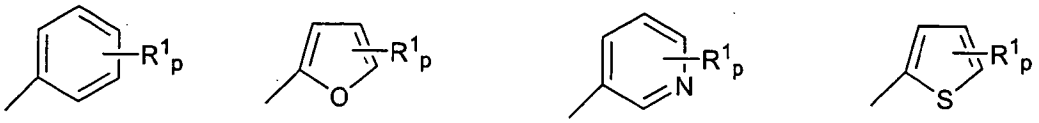
Figure 3



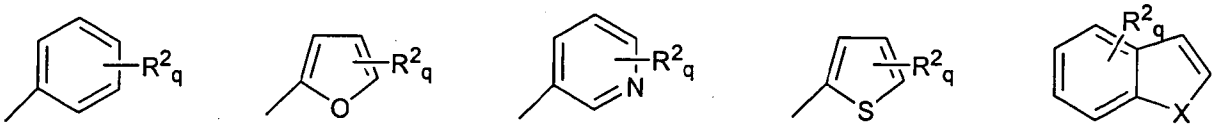
VI

Compounds of Figure 3, Compound Structure VI, preferably having the following structural variations

wherein A is



and B is



and where

n is 0, 1,2,3,4

m is 0, 1, 2, 3, 4

p is 0, 1, 2, 3, 4

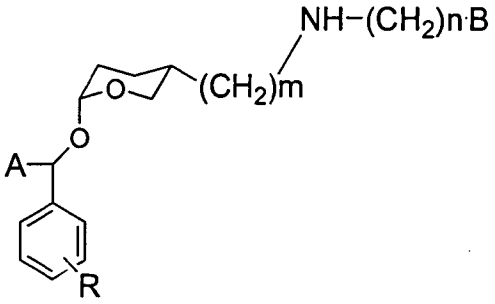
q is 0, 1, 2, 3, 4, 5, 6, 7, 8

X is NH, O, S

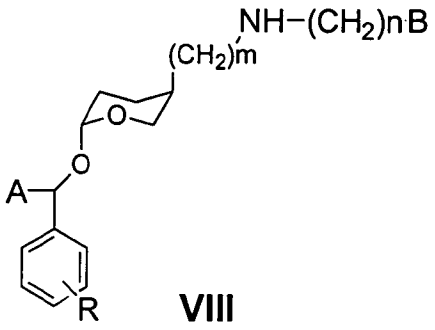
Y is NH, O

R, R^1 and R^2 are selected from the group consisting of H, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} halogenated alkynyl, C_{2-6} hydroxy alkynyl, F, Cl, Br, I, CN, COOEt, OH, NO2, NH2, OR^3, wherein R^3 is C_{1-8} alkyl, C_{5-6} cycloalkyl, or C_{2-8} alkenyl or R^2 is a 5 or 6 membered

heterocycle.and where any carbon of $-(CH_2)_n-$ may be substituted by OR^4 where R^4 is C_{1-8} alkyl or C_{2-18} alkylene, or $-COOR^5$ where R^5 is C_{1-18} alkyl or C_{2-18} alkylene.



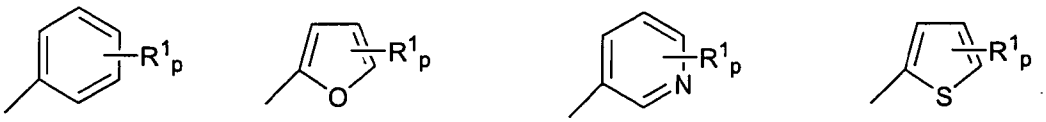
VII



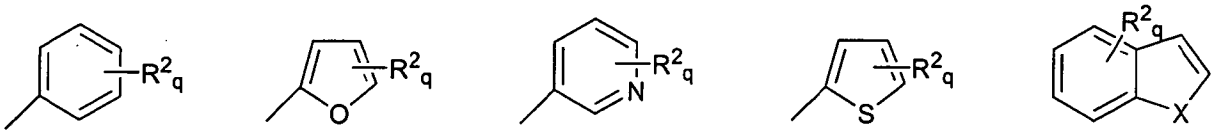
VIII

Compounds of Figure 3, Compound Structures VII and VIII, preferably having the following structural variations

wherein A is



and B is



and where

n is 0, 1,2,3,4

m is 0, 1, 2, 3, 4

p is 0, 1, 2, 3, 4

q is 0, 1, 2, 3, 4, 5, 6, 7, 8

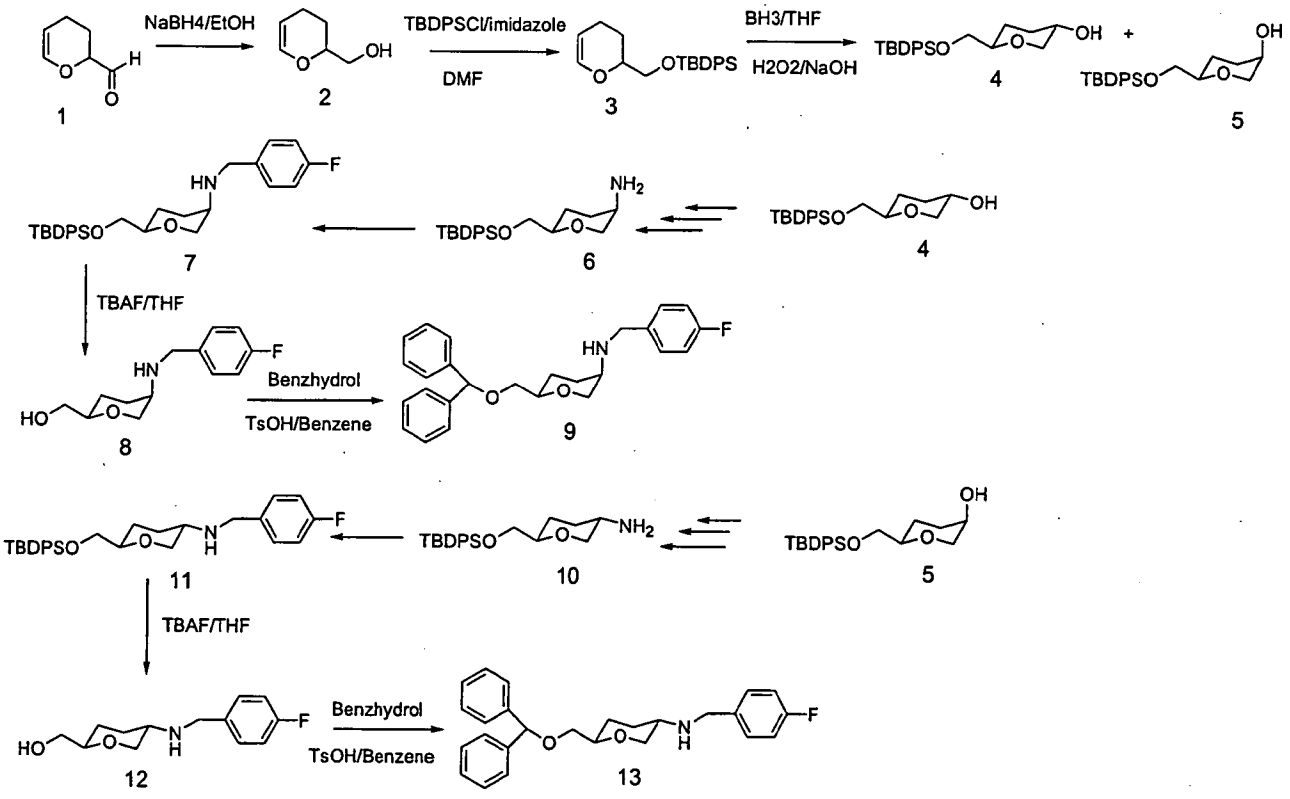
X is NH, O, S

R, R^1 and R^2 are selected from the group consisting of H, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} halogenated alkynyl, C_{2-6} hydroxy alkynyl, F, Cl, Br, I, CN, COOEt, OH, NO2, NH2, OR^3,

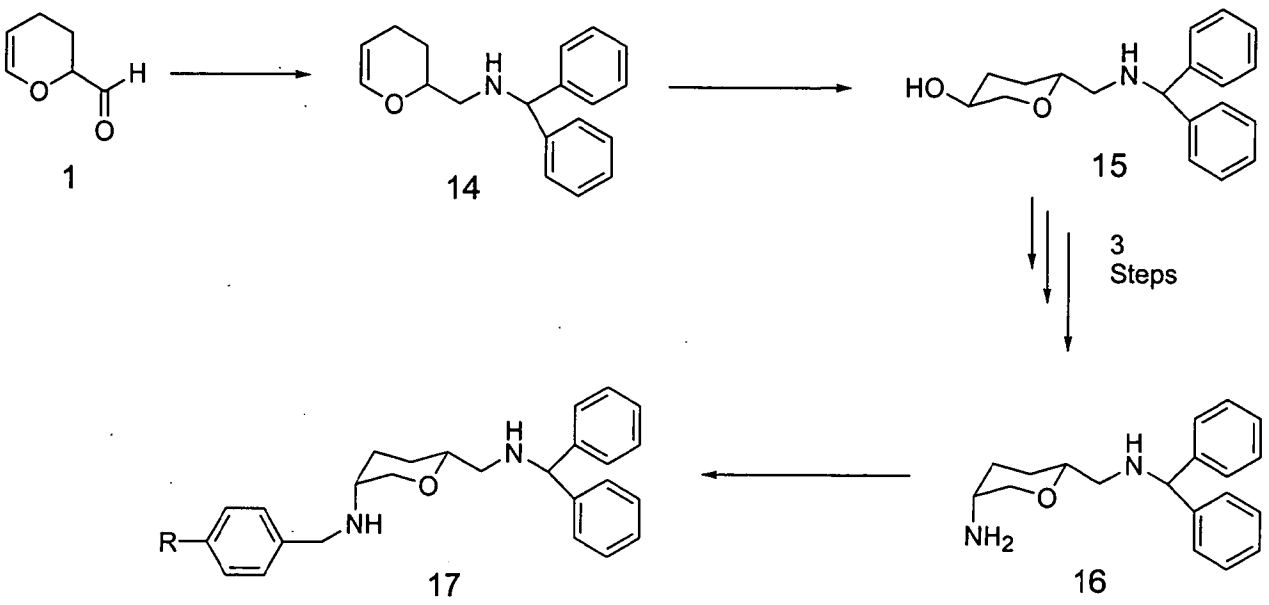
wherein R^3 is C_{1-8} alkyl, C_{5-6} cycloalkyl, or C_{2-8} alkenyl or R^2 is a 5 or 6 membered heterocycle.and where any carbon of $-(CH_2)_n-$ may be substituted by OR^4 where R^4 is C_{1-8} alkyl or C_{2-18} alkylene, or $-COOR^5$ where R^5 is C_{1-18} alkyl or C_{2-18} alkylene.

Synthesis and biological characterization of 2,6-disubstituted pyran derivatives

Scheme 1



Scheme 2



Scheme 3

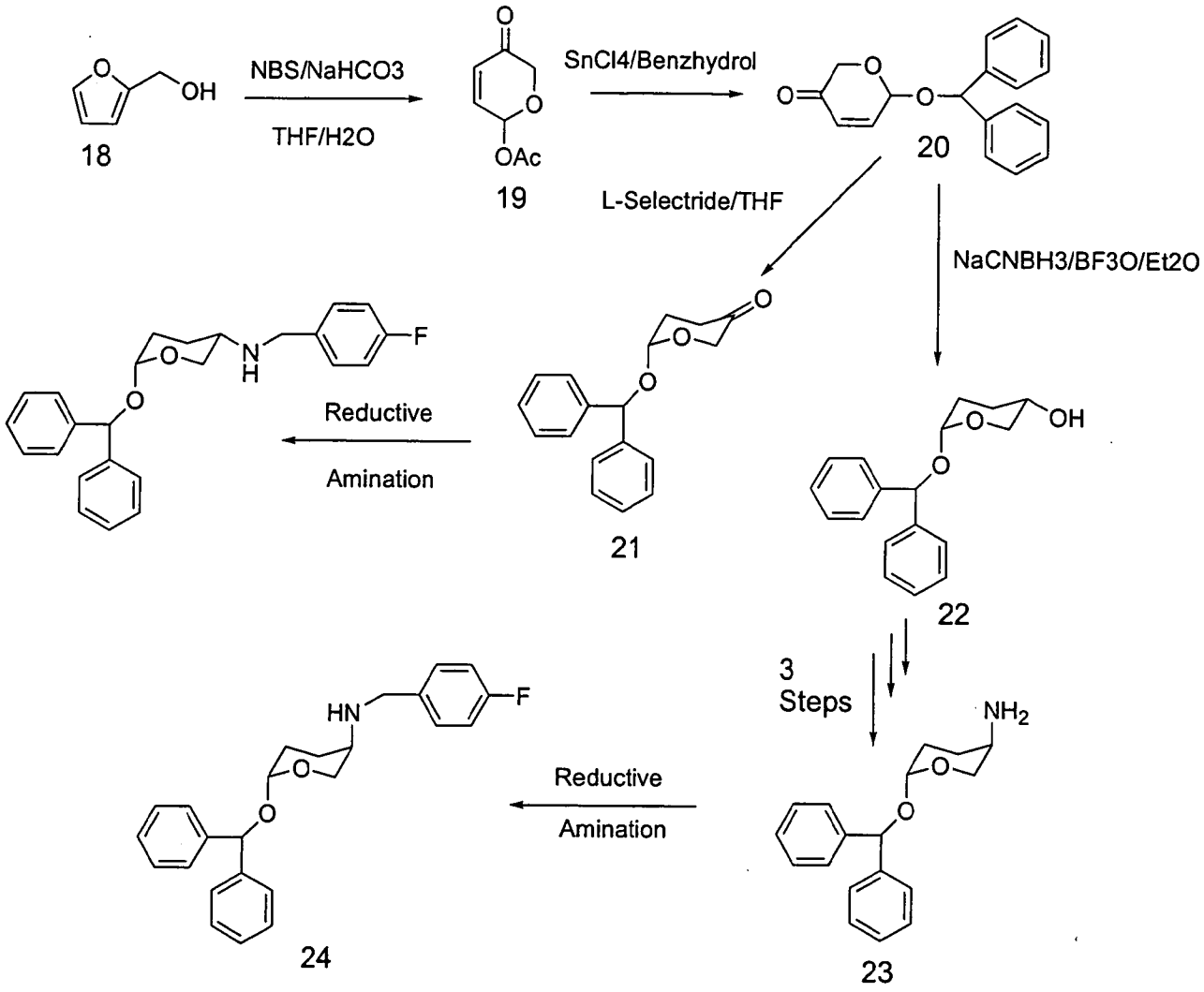


Table 1. Affinity of Drugs at Dopamine, Serotonin, and Norepinephrine Transporters in Rat Striatum.

compd	DAT binding, IC_{50}, nM, [^{3}H]Win 35, 428 [a]	SERT binding, IC_{50}, nM, [^{3}H]citalopram[a]	NET binding, IC_{50}, nM [^{3}H]nisoxetine[a]	DAT uptake, IC_{50}, nM, [^{3}H]DA[a]
cocaine	266±37	737±160	3,130±550	
GBR 12909	10.6±1.9	132±0	496±22	
9	80.4 ± 17.4	>10,000	1328 ± 592	104 ± 49
13	162 ± 19	>10,000	1435 ±	165 ± 17
17	398 ± 33	4400	3432 ± 1752	215 ± 14